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AN EVALUATION OF THERAPY, WITH SPECIAL REFERENCE TO ORGANOTHERAPY*

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The ideal medical treatment is built on the early recognition of disease; an understanding of its causes, its nature; the mechanism of its production, and the development of associated clinical manifestations; a knowledge of the character, extent, and probable outcome of the resulting functional and morphologic changes, and a correct evaluation of the symptoms and of the clinical and laboratory findings. It also demands an appreciation of the indications for treatment, the effect of treatment, and the best methods to employ for the prevention, abortion, amelioration or cure of disease. The goal in treatment can be reached only by the intelligent understanding of disturbed function, and the correction of such disturbance by the application of rational measures. Thus treatment becomes simply a matter of laws, and the "healing art" gives way to a healing science.

It is evident, therefore, that therapeutics is not simply a branch of medicine, but rather the fruit of the medical tree, the culmination of all that science can teach concerning the cause and cure of disease. But the goal is not attained as yet either in the field of general therapy or of organotherapy. Treatment is

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still beset "by débris of broken systems and exploded dogmas." Perhaps it would be well to climb with Holmes his "Monte Testaccio" formed of "the shards and remnant of old vessels which once held human belief," and, as he suggests, gaze about us and broaden our horizons. To our advantage we might at the same time carefully determine the roads of progress in medicine and ascertain so far as possible what is retarding progress in the field of treatment.

Certain features of the landscape stand out in bold relief. Practically all roads of progress begin in the wilderness as bypaths. It is inspiring to look back over the roads that medicine has traveled and to study the lives of those masters, gifted with divine discontent and a spirit of achievement, who with rude axes blazed the bypaths that led onward to the relief of human suffering.

It was a long, dark road from the father of medicine and the versatile Galen to Harvey, the investigator, and to the observant Sydenham. It is since their day that we have learned how science measures, correlates, and advances from hypothesis to law. Therapeutics has not yet shaken off entirely the shackles of empiricism, but the application of law to treatment grows clearer as the cause of disease in illuminated. Disease itself is now recognized, and is treated earlier and more rationally. The therapeutics of today rests on the knowledge of yesterday; the investigation of today will find fruition in the therapy of tomorrow.

Into the chaos of medicinal treatment Schmiedeburg brought order. He gave us methods for the scientific investigation of drugs. As the outcome, we recognize that pharmacologic action is related to chemical constitution, and the field of specific chemotherapy has evolved. The discovery of antiseptics and various anesthetics has transformed a surgical operation from an adventure with death to a sane and safe procedure. Pharmacology has struck from the Pharmacopeia a host of useless drugs, has narrowed the realm of empiricism, and has firmly established relationalism in medicine.

Pasteur's discoveries, especially of the relation of microorganisms to disease, great as they were in their immediate results, set the stage for the greatest achievement of medicine

of all time, the development of preventive medicine, "man's redemption of mankind." Nor without antisepsis and asepsis would we have modern surgery. Studies in immunology paved the way for many new diagnostic methods and for brilliant successes in treatment.

Without a knowledge of oxidation, life and its processes would still remain a riddle. It was left for a chemist, Lavoisier, to demonstrate that "la vie est une fonction chimique." A knowledge of the principles of metabolism, nutrition, growth, and the transformation of energy, is fundamental to biology, physiology, and medicine. The treatment of nutritional diseases demands the consideration of the caloric values of food and their energy exchange values, as well as of the part played by proteins, carbohydrates, fats, water, inorganic salts and vitamins, of which food is composed. Since Addison's day it has been established that metabolism is normally controlled, in part at least, by the glands of internal secretion, and that the disturbance of function of these glands initiates metabolic and nutritional disease. The field on which he threw the first glimmer is now broad enough to demand the earnest consideration of our entire profession, and the particular attention of such societies as ours.

In Virchows's cellular pathology the medical profession found a valuable anchor. It terminated that continuous and hopeless drifting, and inaugurated the fruitful investigation of organic disease. But any conception of disease, confined to structural and organic changes, is out of harmony with the facts and is also unsympathetic, if not actually antagonistic, to drug therapy. Such a narrow conception is responsible, to a large extent, for the therapeutic nihilism of the last generation. Already, recognition of functional elements and an appreciation of the part they play in disease have led to many successful methods of controlling deranged function. In fact, in many instances, not only the presence and extent of disease, but the efficacy of its treatment, is gauged today by tests of functional capacity.

No discovery in medicine, or any other science, sprang full-fledged, so to speak, from the loins of Jove. Each was the sum of earlier discoveries, added to and elaborated by, compre-

hending and original minds. Each master achieved less than the whole of his work, but often vastly more than he anticipated. From Newton, Liebnitz, Dalton and Maxwell, to Watts, Stephenson, Fulton and Edison, from Franklin to Marconi, from Curie to Rutherford, from Crooks to Roentgen; no work is ever complete, and when tired hands put it down, others pick it up. So interwoven are the threads of science that they all appear in the pattern of medicine. The energy of the steam engine is the energy of life; the law of the retort is the law of function; the struggle for existence throws light on disease.

The roads are still far from smooth, and progress is not unfaltering. Human incapacities and frailties, and professional limitations are more serious obstacles now than when progress depended only on the front line of workers. We can readily see that our forefathers erred in assigning the cause and cure of disease to supernatural agencies, in adopting speculative philosophy rather than the methods of science, in adhering blindly to authority, and in their persistent use of remedies about which they knew little, for disease about which they knew less. Yet which of us, being "wholly without sin," may venture to cast the first stone? It is more profitable and more just to visualize the chief barriers to advancement as they exist today, more especially those that retard progress in the field of treatment.

Our diagnostic limitations prevent us from recognizing, and hence treating, disease in its earliest stages. Function is usually disturbed before form is altered, and, obviously, deranged function is more easily corrected than altered structure. In not appreciating nature's defenses, the "vis medicatrix naturae," medical judgment has incorrectly gauged the results of treatment, and most of our therapeutic statistics have been vitiated by lack of adequate controls. The adaptation of measures of relief to the correction of deranged function necessitates a knowledge of the curative agent, as well as of the nature of the disease.

The failure of the leaders in medicine to show leadership in therapy is probably the chief cause of the therapeutic limitations of the profession. Only harm can follow further dependence on dictators in medicine. The leaders must show such breadth of vision, such comprehension of the whole field of medical science, as will stimulate the rank and file to emulation.

Not only the fruits of science, but science itself, must be the handmaiden of everyday practical medicine. The need is more pressing in therapeutics than anywhere else because treatment is set apart from pure science. Pharmacology stands too much alone. Therapy should carry behind it all the driving power that science can command. Only when the pharmacologist is brought to the bedside can he adequately test his theories in practice, in the flame of medical science. The internist should open the field of therapy to science and to scientists. Progress in therapy demands first-hand knowledge of its problems on the part of pharmacologists, physiologists, biochemists and physicists in order to obtain the most effective form of co-operation.

A physician fails individually as he falls short of the standards of his time. Lack of critical judgment or credulity in matters of therapy is, I believe, the chief cause of individual failure. Credulity is, in its essence, lack of wisdom; the physician who has failed may have received inadequate training in therapeutics. But more frequently he lacks the scientific habit of recording treatment and its effects, of measuring it objectively, and of checking his conclusion by controls. Sometimes he is constitutionally too optimistic and sees only the silver lining of the cloud of statistics. As often as not, he has used all his strength for the daily round and has none left to take to his "armchair of cogitation." Therapeutic judgment would be inestimably benefited by attention to these crucial matters, particularly the need of using accurate measurement whenever possible. Otherwise, although clinical observations may be very accurate, they cannot be utilized for further comparison. Laziness, slothfulness and carelessness, love of ease, lack of interest, also contribute prolifically to failure at times, but fortunately these are not common frailties among the practitioners of medicine.

The most pernicious influence in modern therapy comes from without, rather than within, the medical profession. Our best pharmaceutical houses attempt to meet the needs and supply the demands of modern scientific medicine, but there are still certain so-called pharmaceutical firms engaged in a most fraudulent exploitation of the medical profession and the public, in their greed for money. As a result, the physician finds himself

bombarded constantly by advertising matter, reeking with half truths and pseudoscientific patter unless he maintains a high threshold of suspicion he is likely to be seduced by these alluring falsehoods. Ridicule, as our weapon, does not suffice, for it falls unheeded on the thick skin of those who, in the guise of benefactors, betray the sick. The loathing of the conscientious physician should indeed break forth in a demand for federal investigation of much of the advertising material that comes to our desks. It would perhaps be difficult to prove intent to defraud, but it is a matter of right or wrong, and if willfully wrong should lead to prosecution. If prosecution is impossible we may at least notify those in authority and in the meantime use our waste baskets more extensively. Should we not in this Association establish through our official publication a department in which the duplicity and devious devices of these promoters and exploiters may be made apparent to the interested reader, as well as to responsible officials? Such a department could also serve to guide physicians in matters pertaining to organotherapy.

Endocrinology, as we know it, is a young science, but it has its roots in medieval lore. We observe medical history in the act of repeating itself. There is a tendency to bring endocrinology down to the level of the "conjectural art" of Celsus. We see endocrinology a fertile and recently discovered territory, with here and there patches undergoing cultivation; and already, under scientific leadership, several splendid avenues of progress leading to successful treatment. Still, vast areas are unexplored and uncharted. The same old influences are at work here, retarding, or even obstructing, progress. Advancement depends on a careful survey of the situation and the removal of all obstacles.

The glands of internal secretion are concerned with growth, development, nutrition, and metabolism. They may be looked on as "regulators of metabolism," but in regard to the exact function of these glands, we have a few facts and many fancies.

The outstanding established facts of endocrinology may be summed up in a few words. These glands elaborate one or more active principles which effect physiologic activity. The hormones, or active principles, are excreted in each instance into

the circulation and exert a specific action elsewhere in the organism. Disease of one of the glands may lead to increase, decrease, or disturbance of its activity, and this in turn may be manifested by acceleration, retardation, or perversion of physiologic functions in the organism. Disease may result from a lack of a specific hormone and, in certain instances, may be cured by its replacement with one of the same character; or an excess of hormone may cause disease which at times may be amenable to treatment through surgical procedures.

Investigation and discussion in this field have centered also about the possibility of correlated interaction or what might be termed pluriglandular interplay, and whether the various active principles act reciprocally, synergetically, antagonistically, or vicariously. Recently the question of modifying the nature of the active principles of the gland has come into the foreground.

In spite of the volumes written on the subject of organotherapy, only one principle of treatment, as Billings has said, has proved entirely successful in practice, and that is the replacement of a partially or completely missing hormone by one of the same nature. Although this method has been successfully applied to at least three or four diseases, it is not effective as yet in all diseases which are due to glandular deficiency. In this field splendid success has been attained with thyroxin and desiccated thyroid in the treatment of myxedema or cretinism in the young, with insulin in the treatment of diabetes, and with the extract of the posterior lobe of the hypophysis in the treatment of diabetes insipidus. Parathyrin promises equally good results in tetany, but even in these diseases treatment must be continuous. The only glandular substances uniformly effective when administered by mouth are those of the thyroid and the desicated gland, thyroxin. It should be admitted that beneficial results seem to be obtained at times in fields other than the three already mentioned, as for instance, in the treatment of Addison's disease by the Muirhead method. In such fields there exists legitimate opportunity for controlled experimentation, and such treatment must be looked on as more or less in an experimental stage. The results, good or bad, afford legitimate material for publication.

Certain glandular products, besides specifically influencing the organism, also possess definite pharmocologic properties which render them of unquestionable medical value, as, for instance, epinephrin, which stimulates the sympathetic nerve endings, and the extract of the posterior lobe of the pituitary which constricts capillaries.

In the field of organotherapy, too, progress is retarded by human frailties and professional limitations. Replacement or substitution therapy might have a much less restricted field of usefulness if it were not for those diagnostic limitations which make the evidence of deficiency in one or more glands difficult to recognize. Then we cannot be certain that the substance isolated from the gland represents its true, unaltered, active principle. Indeed we are not always certain that alleged products are even obtained from the glands in question. The dosage is bound to be inaccurate, and cannot be adjusted to the fluctuating needs of the organism, especially when the composition and potency of the preparation are uncertain. The greatest obstacle of all is the impossibility of copying nature's continuous administration of glandular products to meet the changing needs of the organism.

The attempt to control the overactivity of one gland by augmenting the action of another that may be antagonistic may be sound in principle, but so far it is scarcely more than speculative, and it is but little justifiable to expect the extract of one gland to correct functions that are not known to depend on that gland. Giving thymus substance for hyperthyroidism is not rational except as an experiment and even then should be preferably restricted to laboratory practice. But in fairness, it must be admitted that the improvement in general metabolism, resulting from thyroid medication, may at times indirectly correct underfunction on the part of the organism as a whole, and also perhaps of certain other glands of internal secretion. There is surely some connection between these organs, not understood, and sometimes quite remote. There is little consistency in the results obtained by most of the groping experiments in organotherapy, in spite of the statements in those very widely read, if unofficial, journals dedicated to human credulity. The methods

of Kendall, Banting, Collip, and Abel, more surely lead to success.

In organotherapy, human frailty looms large. Unfortunately, it must be admitted that in no other branch of medicine has its retarding and pernicious influence been more apparent than in the treatment of diseases of the glands of internal secretion. But the outlook in organotherapy is most hopeful. Success in its limited and legitimate field has been striking, in fact, little short of miraculous, and so encouraging that the field is now ardently exploited, both legitimately in the search for the elucidation of disease, and criminally by those who squeeze gold out of human heartaches. If we are to protect the public against unseasoned and immature conclusions, we must depend on reliable information only. Information concerning standard drugs can be obtained from the United States Pharmacopeia. New drugs of promise, introduced in an ethical manner, are accepted almost without delay by the Council on Pharmacy and Chemistry of the American Medical Association, and are listed and described in one of its annual publications, "New and non-official remedies." Old and new ethical drugs, which are useful and reliable, are described in a small book, "Useful Drugs," also published by the Council. The most flagrant offenders are exposed in the column of the Journal of the American Medical Association under the heading, "Propaganda for Reform," under "The Bureau of Information."

The Council was created by the American Medical Association more than twenty years ago, with the idea of furnishing to physicians reliable information concerning drugs. Advertising space of the Journal of the American Medical Association and of most of the standard medical journals of the country is reserved for preparations accepted by the Council. Physicians are therefore safe in accepting such preparations as are advertised in the pages of the Journal of the American Medical Association, or in other high standard journals. Houses exploiting questionable and nonethical drugs, forced to adopt devious measures of advertising to reach the physician, flood him with circulars, pamphlets, and journals—so-called house organs—published by themselves.

The whole question of organotherapy has been very recently reviewed in a booklet containing the series of excellent articles that appeared in the Journal of the American Medical Association. The physician also must know where to secure these reliable drugs. The same publications contain sufficient information, if it is followed, to prevent the foisting of spurious products on the public. In specifying the products of particular firms, it is well to choose products of well established houses who advertise in the best journals and who are engaged in meeting the demands of the medical profession. The products of mercenary concerns who advertise in circuitous ways, who willfully misrepresent, and who attempt to create fictitious demands, should be shunned. Above all, flagrant boasters should be avoided, for, as Voltaire says, "It is only the charlatan who is certain."

There are a few simple rules to guide the general practitioner in the treatment of diseases of the glands of internal secretion. Glandular products should be used only as they are scientifically indicated, that is, as substitutional or replacement therapy. A single product of the gland concerned is to be given. This may suffice, provided the diagnosis is correct, the product potent, and properly administered. Fixed pluriglandular mixtures for so-called multiple glandular deficiencies are to be avoided. The practice of administering such mixtures constitutes a disgrace to twentieth century medicine, a menace to our profession, and a betrayal of our patients. When it is considered that the indications call for more than one principle, the second glandular product is administered in gradually increasing quantities. Accurate records of treatment should be kept and the results measured objectively.

As long as disease holds its challenge for prevention, abortion, amelioration and cure, the forces of investigation must toil on. The goal will only be reached through an intelligent understanding of disturbed function and the application of rational measures for its correction. The day is past when the student in the ward or the scientist in his laboratory may hope to expose the whole story of disease. The world of illness is our laboratory; science cannot be pre-empted. MacKenzie rose to eminence after carefully watching disease in his community for

many years. Any physician, a village doctor for half a lifetime, may be called to leadership if he uses the methods of science. MacKenzie never ceased to preach the need of enrolling the general practitioner in the army of progress. He deprecated the narrow conception of disease that comes only from viewing the end result through a microscope. His efforts to the last were concerned with the attempt to demonstrate the practical value of understanding early symptoms. As with diagnosis, so with treatment. The response of advanced disease to therapy is comparatively easy to determine; the response of disease at its inception cannot be studied in the wards alone because the hospital never hears the plaint of the slightly ill. In treatment, now more than ever, progress depends on the co-operation of every member of our profession in the application of the methods of science to the problems of medicine.

CIRCULATORY DISTURBANCES IN DISEASES OF THE GLANDS OF INTERNAL SECRETION*

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However obscure the functions of the endocrine glands may be we can agree, I think, that they are all concerned in one way or another, direct or indirect, with metabolism. If this is so, we must assume that they are likewise all concerned with the circulation, for in all except very lowly organisms the metabolism of tissue cells is vitally dependent upon a free supply of a suitable circulating medium. If the secretions of endocrine glands influence cell activities, they must of necessity also influence the supply of the medium upon which such activities depend. While the study of the exact mode of action by which such influence is brought to bear belongs properly to the physiologist or pharmacologist, it is altogether pertinent for the clinician to seek to interpret, in the light of knowledge gained by such studies, the circulatory disturbances which he may observe in patients known to be suffering from endocrine disease.

The actions on circulation which the several hormones may conceivably possess can be variously grouped. For convenience we may separate them into those affecting primarily the heart, the vessels, or the blood. Effects primarily on the heart may be manifest in the force, frequency or rhythm of the heart beat; those primarily on the vessels in the total or regional cross section of arteries, capillaries or veins; and those on the blood itself in its total quantity, viscosity, concentration, or ability to transport the respiratory gases.

To identify these effects in the patient, we are dependent upon the inferences which can be drawn from such factors as we can actually observe, measure and record. In man, for example, we can count the pulse, analyze cardiac conduction, and directly determine blood pressure, blood viscosity, and the chemical composition of the blood. Methods are also available for calculating indirectly the blood flow, both total and regional,

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and the total volume of blood in the body. The gas exchange and the vital capacity of the lungs can also be measured and will often throw light on the subject in hand.

It is impossible in the short time allotted to this discussion to do more than indicate the general nature of the problem. Let me, therefore, by way of illustration, start with the consideration of the hemodynamics of thyrotoxicosis and myxedema, these being the endocrine disorders in which circulatory disturbances are the most striking.

The outstanding functional alteration in thyrotoxicosis is an increased, and in myxedema a decreased, rate of metabolism, due on the one hand to an excess, and on the other, to a shortage of the thyroid hormone, thyroxin.

The increased metabolism of tissues in the hyperthyroid individual will necessitate increased circulation, and it is the degree, manner and results of this increase that now concern us. On the ratio between metabolic rate and pulse rate there are extensive data in the literature (1, 2, 3). In general it may be said that there is a certain parallelism between the two. The results obtained by Minot and myself, which seem to be like those of other observers, show that, speaking of course in terms of averages only, for a rise of 50 per cent in metabolic rate there is a rise of about 65 per cent in the pulse rate. It was found also that the same sort of relationship held in leukemia, another disease strikingly characterized by increased metabolism. In contrast to this, it was found that when in a normal subject metabolism rate increased 50 per cent by the performance of muscular work, the pulse rate increased not more than 25 per cent (4). This is of some interest as showing that either the mechanism or the magnitude of circulatory response to metabolic rate increase may be different in health and disease.

The pulse rate, however, gives us no certain information of the actual magnitude of circulation rate increase. The amount of blood expelled by the heart per minute depends not only upon the rate of beat, but upon the amplitude of beat as well. These may vary independently. In the normal person when metabolism goes up due to the performance of muscular work, the circulation rate, that is total blood flow per unit of time, roughly parallels it, as though any increase in demand on the

part of tissues for oxygen was taken care of by a proportional increase in the supply of blood. At least this is so for milder grades of work. As work becomes heavier, the circulation rate tends to lag behind the metabolic rate, with the result that relatively more oxygen is removed from the blood in transit through the tissues. The increased blood flow with work in normal persons is accomplished partly through an increase in rate of beat, and partly through an increase in the volume expelled per systole (5).

There are but few data in existence on the blood flow in thyrotoxicosis. Field and Bock (6), at the Massachusetts General Hospital, during the past winter have made some observa-

TABLE 1

*Blood Flow at Rest**

DIAGNOSIS	CASE	BASAL METABOLIC RATE PER CENT	BLOOD FLOW LITERS PER MINUTE	PULSE RATE	OUTPUT PER SYSTOLE C.C.
Normal	Average	....	6.3	62	101
Exophthalmic goiter	P	+60	8.9	104	86
	B	+60	14.0	93	150
	O	+72	11.8	102	116
	G	+69	12.0	106	113
	Average	+65	11.7	101	116
Myxedema	W	—28	2.8	48	58
	M	—27	2.3	55	43
	Average	—27.5	2.55	51.5	50.5

*Field & Bock.

tions in both Graves' disease and myxedema, which they have been kind enough to let me quote to you now. Their observations were made by their modification of the Fick principle of blood flow calculation. The figures obtained in normal, thyrotoxic and myxedematous subjects are shown in Table 1. While owing to the lack of sufficient knowledge of the minute volume of the circulation during rest in normal persons it is impossible to state with exactitude the per cent increase in blood flow for a given rise in basal metabolic rate in hyperthyroidism, still, on the basis of the data in Table 1, it is legitimate to draw the general conclusion that there is a distinct rise in blood flow, which at least equals, and more probably exceeds, the rise in metabolism. Somewhat similar conclusions have been reached by Davies, Meakins and Sands (7). In myxedema a reverse condi-

tion was found. That is to say, the blood flow showed an even greater retardation than the metabolism (Table 1).

It seems, therefore, that if in the normal person because of the performance of muscular work, or in the patient with Graves' disease because of excess of thyroxin, the tissues call for an increased supply of oxygen, the circulation responds to the demand adequately, that is, with an increment apparently somewhere nearly proportional to the increment in demand. The work-induced circulation increase of the normal person, however, is brought about by an increase both in pulse rate and amplitude of beat (output per systole), whereas, in that resulting from hyperthyroidism, the increased heart output seems largely to result from increased pulse rate alone, the output per systole showing a less striking tendency to rise.

The cause of this difference is food for thought. The suggestion is obvious that in hyperthyroidism asthenia of the myocardium, or a toxic effect of some sort, interferes with increase of amplitude of contraction. It has been fairly well established that in the case of the respiration the total amount of air pumped is controlled chemically through the pH of the blood, but that the rate and type of breathing is subject to nervous control. Since the circulation subserves the same purpose as the respiration, it is entirely possible that its method of control is the same; that is to say, as suggested by Boothby (8), the total blood flow is regulated chemically. The rate and amplitude of beat, however, to follow out the analogy, would be governed through the nervous system. Field and Bock have made two observations on the effect of atropine. Here, although the pulse rate was markedly increased, there was little or no change in blood flow, and therefore a marked diminution in output per beat. This is of some interest as being, perhaps, an instance of a purely nervous effect. It is in contrast to the result obtained in dogs by Harrison, in which it was shown that the injection of acid increases minute volume. The action of atropine, paralysis of the inhibitory fibres, is of course similar to stimulation of the sympathetic or accelerators. It is believed that some of the symptoms of exophthalmic goitre are due to excessive sympathetic activity, and it well may be that in that lies the explanation of the failure of the systolic output to increase in that dis-

ease. Whatever the cause, the result, namely the wastage of cardiac effort incident to the increase in number of systoles and the accompanying encroachment on diastole is obvious.

Arterial blood pressure is easier to determine, but less easy, perhaps, to interpret than blood flow. The pressure in the arteries is the resultant of two independent variables, heart output and peripheral resistance. The latter is again separated into the viscosity of the blood and the total cross section of the arteriolar bed. Read (3) has devoted particular attention to the relation between pulse rate, pulse pressure, and basal metabolism, and finds that departures of the latter from the normal, whether above or below, are closely paralleled by both pulse rate and pulse pressure. A somewhat closer correlation still was found between basal metabolism rate and a mathematical combination of pulse rate and pulse pressure.

Also of interest, but still more difficult of interpretation, are some recent observations by Thompson (10) which were started at the Boston City Hospital and now are being continued at the Massachusetts General Hospital upon the blood volume in hyper- and hypo-thyroidism made by the vital red method of Keith, Rowntree and Geraghty (11). In brief, Thompson's findings show that in hypothyroidism there tends to be a diminished, and sometimes in hyperthyroidism an increased total volume of blood plasma. Furthermore, in myxedema when thyroid is administered, volume rises, and in an exophthalmic goitre patient during an iodine remission, it fell. It would seem, in other words, as though the total quantity of available circulating medium varied with the magnitude of the demand for circulation.

Let us now, for the sake of comparison, pass for a moment to the hemodynamical action of adrenalin in normal persons. This, after thyroxin, is the endocrine hormone most definitely possessed of a calorigenic action (12). Field and Bock, however, have been able to show that, unlike thyroxin, it has an augmenting action on blood flow that far exceeds its calorigenic action. For example, in four cases of exophthalmic goitre an elevation of 65 per cent in the basal metabolism rate was productive of an elevation in blood flow approximating 85 per cent. While in a normal subject injected with 1.5 cc. of adrenalin a result-

ing 20 per cent rise in basal metabolism rate was accompanied by a 94 per cent rise in blood flow, the corresponding increments in pulse rate were 63 per cent in exophthalmic goitre and 46 per cent after adrenalin; the volumes per systole were 16 per cent in exophthalmic goitre and 33 per cent after adrenalin.

In appears, therefore, that the metabolic rate increases are accompanied by blood flow increases of varying degrees. In muscular work blood flow just parallels or falls somewhat short of metabolic increase. In hyperthyroidism blood flow parallels or somewhat exceeds metabolism, and after adrenalin injection it very markedly exceeds metabolism. In muscular work and after adrenalin there is an increase in both rate and amplitude of heart beat, while in hyperthyroidism the increase in rate is the more striking of the two.

The relative changes are indicated in Table 2, where all the factors are expressed as per cent deviations from normal rest-

TABLE 2

*Blood Flow Rates**

CONDITION	SUBJECT	BASAL METABOLIC RATE PER CENT	BLOOD FLOW PER CENT	PULSE RATE PER CENT	OUTPUT PER SYSTOLE PER CENT
Muscular work.....	Normal (J.H.M.)†‡	+65	+55	+23	+25
Muscular work.....	Normal (H.F.)..‡..	+65	+42	+12	+30
Exophthalmic goiter.	Average (4).....	+65	+86	+63	+16
Adrenalin injected..	Normal (H.F.)..‡..	+20	+94	+46	+33
Myxedema.....	Average (2).....	—27	—59	—17	—30

*Per cent variation from resting normal.

†From Means and Newburgh. Experiment on J. H. M. by Krogh and Lindhard's Method. All the others are by the Field and Bock Method.

‡Variations expressed in percent above or below subjects' rates at rest in case of J. H. M. and H. F. The exophthalmic goiter and myxedema series are compared with Field and Bock's averages for normal subjects.

ing values. As stated before, what constitutes normal in the case of blood flow is but imperfectly known, so the table must be accepted as a first approximation only.

One is led to the conclusion in the case of adrenalin that there is an action directly upon the heart itself, increasing its force of beat, and that peripherally there is vasodilatation. Were there not vasodilatation with a 100 per cent increase in minute volume there would be a sharp rise in blood pressure, but there is not. In the experiment on H. F. systolic blood pressure rose comparatively slightly and diastolic fell. One also suspects that thyroxin may exert a similar action, but to a very

much less degree. With regard to adrenalin, such a conclusion does not preclude vasoconstriction in certain regions. The conclusion is simply that the sum total arteriolar effect is a widening. Constriction of skin and visceral vessels, for example, might be completely offset by dilatation of those of musculature (13). Adrenalin must likewise have had an effect upon the heart itself, for it does not seem possible to explain the great increase in minute volume by increased opportunity for arteriolar escape alone.

The effects which such hemodynamical alterations may exert must next attract our attention. A theoretical consideration of cardiac work may prove helpful. The work performed in the pumping action of the heart in the last analysis comes down to the total amount pumped and the pressure against which it is pumped. Thus, in a normal man at rest if the minute volume is six liters and the mean blood pressure is 100 mms. of Hg (which is equivalent to 1.28 meters of blood) the work is $6 \times 1.28 = 7.68$ kilogram meters per minute. In Table 3 this is contrasted with certain pathologic states. The values are assumed, but in view of the known facts, the values as given are reasonable. Either a state of hyperthyroidism elevating the basal metabolic rate to plus 65 per cent, or an adrenalin effect elevating it 20 per cent, will double the blood flow without great change in mean blood pressure, and, consequently will double cardiac work. But so, too, would an arterial hypertension with a mean pressure of 200 and no acceleration of blood flow. In marked contrast is the state of affairs in myxedema in which the work of the heart must be greatly reduced.

In either hypertension or hyperthyroidism there will be, even at rest, a marked increase in the task the heart must perform, and, consequently in each cardiac hypertrophy and later fatigue and perhaps failure. Greater degrees of hypertrophy are seen in chronic hypertension, but this may be because hypertension lasts longer than hyperthyroidism. Or the heart may fail sooner in hyperthyroidism because, though the extra load may be no greater than in hypertension, the more rapid rate gives less time for rest. White and Sprague (14) have recently made some measurements of length of systole in normal and thyrotoxic persons. These show that while in a person with a pulse rate

of 60 the total length of systole per minute may be but 24 seconds, in a thyrotoxic person with a pulse rate of 130 it may reach 35 seconds. Such a shortening in total diastole, if long continued, might alone greatly increase cardiac fatigue.

Whether the thyroid hormone in toxic goitre also exerts an actual toxic effect upon the heart is a matter of dispute. The work of Goodpasture (15) indicates that even if it does not do so directly it at least predisposes the heart muscle to destruction by other toxins.

The actual circulatory symptoms and signs of hyperthyroidism and myxedema are sufficiently familiar to make enumeration here unnecessary. The points that I should like to emphasize are that those of hyperthyroidism are understandable on the basis of the known morbid physiology; that is, rapid metabolism and blood flow and a certain amount of arteriolar dilatation, together with the direct cardiac resultants of long continued overwork and hurry, and finally fatigue and failure. The

TABLE 3
*Cardiac Work**

CONDITION	BASAL METABOLIC RATE PER CENT	BLOOD FLOW LITERS PER MINUTE	MEAN BLOOD PRESSURE MMS.	HEART WORK KGM. PER MINUTE
Normal	0	6	100	7
Hyperthyroid	+65	12	100	14
Hypertensive	0	6	200	14
Adrenalin injected	+20	12	100	14
Hypothyroid	−30	3	100	3.5

*Theoretical.

symptoms and signs of myxedema are in the main the converse and due to converse conditions.**

Of circulatory disturbances in other diseases of the endocrine glands I shall say nothing, for until their hemodynamics are worked out interpretation of signs and symptoms is largely guess work. I may simply mention in closing that in all, doubtless, there are circulatory abnormalities. I need but cite the hypotension of Addison's Disease, and the fact that from the pituitary is obtained a substance for short periods highly pressor in action. The gonads, too, probably have their circulatory action; witness the circulatory disturbances of the menopause. But the

** The myxedema heart recently reported by Fahr (16) is of great interest, but difficult of interpretation.

nature of the mechanism of these is not sufficiently understood to warrant discussion at this time.

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PSYCHICAL DISTURBANCES IN THE DISEASES OF THE GLANDS OF INTERNAL SECRETION*

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The relation of disease of the glands of internal secretion to mental disturbance is no simple problem. For its solution the experimental method is available to but a very limited extent, and we have to take the material supplied by nature, which has little respect for the conditions of an accurately controlled experiment. Before we correlate mental disturbance with endocrine disorder we must have in each case some reasonable degree of certainty as to the nature of the endocrine disorder and a fairly precise analysis of the mental disturbance; even when we are ready to associate in close union the endocrine disorder and the mental symptoms, we must not be surprised should the statistician forbid the banns.

The internist is familiar with the difficulty of establishing in each individual case the exact nature of the endocrine disorder, which expresses itself in the physical structure, the physical symptoms and the reactions to special tests; to the psychiatrist it is not necessary to emphasize the difficulty of giving its due weight to each of the numerous factors, which are liable in the individual case to contribute something to the disturbance of the patient's social behavior, his beliefs, his emotional balance.

In view of these difficulties it is not to be wondered at that so little progress has been made in this special field since Cushing's (1) appeal for co-operative investigation at the opening of the Phipps Psychiatric Clinic in 1913, and I do not know that I have anything substantial to add to the principles laid down in that address.

The first step to be taken is the careful accumulation of cases with unequivocal evidence of a well-defined endocrine disorder. Such cases are usually observed in a surgical or medical service, where anomalies of structure and of metabolism are

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studied intensively, while mental disturbances are apt to receive summary mention.

In "An Autograph History of a Case of Addison's Disease" by A. L. Muirhead (2) we find little mention of the personal factors in the total reaction. Even though the author had given a more detailed account of such personal reactions, it might have been difficult to disentangle them from the general tissue of the personality, woven as the latter is from native endowment and individual destiny, as well as from the single coarse strands of organic function, and after disentangling them to correlate them with the disturbed function of the adrenal glands. In early life Dr. Muirhead suffered from indigestion: "It produced a feeling of weariness, drowsiness and depression that often interfered with his studies. This condition continued, in varying degree, for a good many years and at times caused depression, both physical and mental, almost as marked as Addison's disease does at the present time."

The depression which was observed after the definite development of Addison's disease might be interpreted as symptomatic of disordered function of the adrenal glands, or on the other hand it might be regarded as the reaction to the physical disorder of a personality, whose latent depressive trend had already been elicited by the digestive trouble in the early twenties. Such a depression might therefore be deeply rooted in the constitution of the individual. Without a careful review of the heredity of the patient, and of his early development, the interpretation of the depression as the direct expression of the disordered function of the adrenal glands would be rash. It is true that in the family, as in the patient, traits of personality may be correlated with glandular anomalies. A glandular inferiority may be an outstanding feature in a family stock as has been shown among others by Barrett (3) in relation to the thyroid gland, and by Cushing (4) in the case of the pituitary gland. We are, however, at present seldom able to translate "constitution" into a glandular formula.

The difficulty of correlation of mental disturbances with glandular disorders is further exemplified by Leonard Mark's (5) detailed analysis of his own acromegalic experience, referred to by Cushing in his 1913 address. In this account Dr.

Mark tells in detail of his various distressing symptoms: "When I am at my worst I still seem to be master of all my mental faculties, but lose the inclination to make best use of them. There is some mental depression, but it is overbalanced by the strong feeling that if I can only remain perfectly still for a little while the condition will pass off and I shall be all right." This mental condition is very different from other conditions which the psychiatrist is accustomed to group together under the term "depression," conditions in which there is a feeling of lonesomeness, lack of ambition and hopelessness and in which one sees no preservation of that central confident personality, which looks upon the distressing feelings as something outside of itself. In such conditions the citadel of the personality itself is in the hands of the foe, while in the experience of Dr. Mark the enemy seems still to be without the walls. Had not Dr. Mark had such a stout heart the central personality itself might have surrendered. As a matter of fact Dr. Mark admits the transitory development of such a depressive state when he learns the nature of his disorder. "I must confess that the first effect of the knowledge that I was suffering from such a malady had a most depressing effect upon me and for several days I went about feeling profoundly miserable. The first taste of the fruits of knowledge was indeed bitter; I felt that I should soon grow rapidly worse and dreaded what might be in store for me. I was also exceedingly annoyed with myself for not having made the discovery sooner and felt I must be branded as an ignoramus for not knowing more about acromegaly." These emotional reactions to the complex situation can apparently be definitely separated in the case of Dr. Mark from the previous symptoms, which represent a different type of mental depression of somewhat simpler nature, closely related to feelings of general discomfort and fatigue. It is important in correlating endocrine disorders with mental disturbances to keep in mind clearly the distinction outlined above. It is probable that in the case of Dr. Mark the type of mental depression associated with the fatigue and discomfort was closely related to the pituitary disorder, while the type of depression which, for a short time, overwhelmed him after learning the nature of his disorder may have had no specific relation to the pituitary disorder but was dependent upon

much more subtle and complex functions which are included in the general term personality. It is not suggested that the personality is a metaphysical entity or entelechy apart from the component organs and systems of the body; the personality is a term which includes very complex reactions to which no doubt the pituitary gland contributes its quota like every other component of the body, but one can make a distinction between the reaction of the whole individual to the knowledge that he has an incurable disease of the pituitary gland, and certain distressing feelings recognized by the personality to be as extraneous as feelings of discomfort and fatigue. In disorders of the other glands of internal secretion we meet the same problem. In diabetes we have to consider not only the hormonic influence of the gland but the reaction of the individual patient to the knowledge that he has a serious disease. In the case of a woman who has had double ovariotomy we have to consider not only the endocrine influence on mood and thought and behavior but also the reaction of the individual woman to the fact that she has been sterilized and her whole career has been seriously altered.

Further reference may be made to the interesting case of Dr. Mark. He devotes one chapter to describing various noises in the head—a seething sound, fizzing sounds, a buzzing sound. At the same time tunes were continually running in his head in a not unpleasant way. His symptoms would be more relieved by a sonata of Beethoven than by a dose of antipyrin. The former would soon put him right "and in less than twenty minutes I should be feeling quite comfortable and the head trouble would have been charmed away." In these symptoms, as in the reaction of the total personality to the situation of his disease, we may perhaps see a very large contribution from the individuality of the patient, and must be on our guard against correlating them too directly with the disorder of the pituitary gland. Patients vary not only in their total personality, in their temperament and dominating mood, but also in their sensory endowment, and the total clinical picture is liable to bear the very definite imprint of the special endowment of the individual.

Owing to the kindness of Dr. Cushing it has been possible for me to see a series of cases of dyspituitarism, the larger number of whom were suffering from acromegaly. I have been im-

pressed by the comparatively slight modification of what one might call the central personality and by the fact that the mental symptoms touch so little the emotional ground work of the personality; one meets variation in output of energy and various slight changes of mood, either expressive of the special constitution or in reaction to the special life situation which the disease has created.

A young woman of thirty-two, always slightly self-conscious, since the development of her acromegaly had shown a natural sensitiveness to the change in her physical condition and a corresponding degree of seclusiveness. She showed no definite depression and was less inclined to have blue spells than during her girlhood. She still enjoyed to a normal degree musical and intellectual opportunities. She was subject to periods during which she would feel that she had less initiative and had to urge herself to do things. She formulated the influence of the disease on her mental state as "a simplifying—I don't care to be as analytical as before, I am quite willing to let things take their course, to drift along." In such a case we are reminded of some of the symptoms of Dr. Mark, of his feeling of fatigue, his desire to keep still, his disinclination to make the best use of his mental faculties. and as in the case of Dr. Mark the symptoms come and go. There are times when she has as much energy and enthusiasm as ever. She feels no slowness in her thought even when she is slow in her movements.

An Armenian of forty-seven with acromegaly would have bad dreams. Later he developed episodes during which his mind passed into a peculiar condition, although he was not unconscious. A five-minute nap would put him all right. In this patient one saw no alteration of the fundamental mood—he was placid and not depressed; he felt that his memory was not so good and that concentration was a little more difficult.

A rather simple Irishman of fifty-six with chronic myocarditis seemed to take his acromegaly in the most matter-of-fact way.

A woman of forty-eight with acromegaly had shown progressive blindness; at first she had cried a little about this handicap, but had shown no other depression At times she would have a feeling of being afraid to be alone. She had periods when she would be slower in her activity than usual. She complained of "slowing up of cerebration" and said that she was very forgetful. In this case we see a patient reacting courageously to her blindness and to the slight difficulty of her thought processes. Morbid fear may have many sources and one would hesitate to associate it directly with the dyspituitarism.

A steamfitter of forty-four with acromegaly complained of his head occasionally becoming confused so that he gave up driving his car on Sunday. Ten years previously he had become more irritable, but after a year he improved in temper owing to his wife's admonitions. At the time of examination one saw remarkably little modification of the personality; he reacted to the situation in a very matter-of-fact way; his only complaint in regard to mental functions was that it took him a little longer to grasp things.

A woman of forty-eight with acromegaly showed a remarkable preservation of normal interests and a very even disposition, although suffering from headache and progressive weakness. There was a certain slowness in her reactions and she was somewhat depressed over the fact that so little could be done for her severe headaches.

In the above cases of dyspituitarism of the acromegalic type one notices practically no primary disorder of mood, no changed attitude towards life, variable loss of energy and initiative, occasional complaints of lack of concentration or forgetfulness.

If one turn from the acromegalic type of dyspituitarism to the large group of cases where hypopituitarism is suspected one has a most complicated group of cases to deal with; in such instances the exact rôle of the pituitary gland may be somewhat obscure and the total analysis of the personality forms an important part of the investigation. A very partial view of the situation is apt to be obtained by the individual worker, owing to the circumstances which determine the material which comes under his observation. The psychiatrist to whom patients are brought on account of lack of intelligence or difficulty of behavior will tend to overestimate the frequency of such defects in patients with hypopituitarism. In cases presenting Froehlich's adiposogenital dystrophy, mental retardation and anomalies of character and behavior are frequently observed by the psychiatrist; on the other hand, these mental anomalies show little of specific nature so far as I am aware and similar personal traits may be observed in other types of constitutional inferiority. It is possible that in patients of the Froehlich type, with mental anomalies, the mental and physical disturbances may be parallel manifestations of some developmental flaw, and the mental disturbances need not be secondary to the endocrine disturbance.

An interesting type of dyspituitarism is furnished by certain children who are physically very immature, but who may be bright and intelligent, even precocious.

An example is a boy of fourteen with the physical development of a boy of about eight. His mental age as determined by standard intelligence tests is that of the average boy of seventeen. His conversation has the formal precision of the youthful Macaulay, answering the kind inquiry as to his toothache with: "I thank you, madam, the agony has abated." The patient occasionally plays ball: "I take advantage if allowed the opportunity." His attitude towards girls is formulated as follows: "There was a certain lady back home who had something of an attraction for me." This patient of Dr. Cushing recalls the case he has reported of the girl nine years of age who "behaved like a prim little old lady."

The field of thyroid disorders is perhaps less complicated than that of pituitary disorders and the interpretation of the

cases is not complicated by the dual nature of the gland. The presence of mental disturbances in thyroid disorders is very familiar but the subject requires a great deal of further study. Superficial resemblances are often made the basis of seductive hypotheses. The contrast between the energetic activity of the case of hyperthyroidism and the slowness of the myxedematous patient has led to the facile suggestion that in the alternations of elation and depression in the manic-depressive condition we have the expression of a recurrent thyroid disturbance. The close scrutiny of the actual nature of the disturbance in definite thyroid disorders makes one hesitate to accept the analogy.

A woman* in the forties had for several years since the death of her husband been very nervous. Two years before thyroidectomy she would wake up at night with the feeling of someone in the room; she would be afraid to draw a breath "lest they hear me." She would then bolt for the children's room and get them to search the house. Even before her husband had died she was too nervous to live on the first floor, she would be unable to sleep until he came in. For some time before thyroidectomy she showed the restless energy and lack of placidity characteristic of hyperthyroidism: "It seemed I had to be doing something all the time—I would say, I'll sit down, but I had to be up again." She found it difficult to sit and read the paper; she could not concentrate if anyone were talking. Before correlating the emotional state of the patient directly with the hyperthyroidism it is well to note that at the age of twenty, after three years in the United States, she had a period during which she was "all tired out, had no ambition; I felt a little nervous; I would jump if the bell rang." It is possible that such an episode has to be formulated in terms of the total constitution of the individual and not in terms of merely one gland, and in her later mental symptoms we have to weigh the contribution of her special constitution as well as the influence of the hyperthyroidism. Certain episodes in her life may also have tended to reinforce a tendency to fear, for her husband was a policeman and had been twice seriously assaulted.

A married woman of twenty-seven had been quite fearless previous to her mother's death, when she was twenty-four. She was active, ambitious, irritable, domineering. With the development of definite hyperthyroidism, she showed in her mood an accentuation of her previous traits. She was more domineering and sensitive and had less control of her reactions. There was no special feeling of depression. The slight restrictions of hospital life led to tantrums, tears, and protests. She felt restless, and before admission to the hospital had carried on an unnecessarily full programme of domestic and social activities. Concentration was difficult; she would force herself to read one page ten times. Her sleep was disturbed as she felt so fidgety. The eager talkative condition of such a patient has a superficial similarity to the excited phase of a manic-depressive patient, but there are also points of dissimilarity. The mood cannot at once be identified with that of the manic patient, although the

*I take this opportunity to thank Dr. Christian, Dr. Sturgis and other members of the staff of the Peter Bent Brigham Hospital for allowing me to study the cases referred to.

latter may vary from definite euphoria to marked irritability. The over-activity of the manic patient is apt to be futile and exuberant and has frequently lost the normal purposive quality, which is retained in the case of hyperthyroidism. The patient referred to above was very talkative, alert, commenting on a variety of topics. There was no tendency, however, to pun or to rhyme; in the talk of the patient, as in her behaviour, the purposive or adaptive quality was still retained, while in the manic excitement it is seriously diminished if not altogether lost. The family history of the patient was of some interest: her paternal grandmother, her father and three out of the five siblings having very hasty tempers; the mother was subject to recurrent spells of depression. The question may be raised as to the rôle played by the thyroid gland in the constitutional explosiveness of her relatives and as to how far her own early eager, energetic, ambitious temperament was largely conditioned by her thyroid endowment.

In the above case the emphasis has been laid upon the restless activity of the patient, her mood, her inability to concentrate, her original constitution. One may refer to these factors in a few other cases of hyperthyroidism. One woman who has just remarried admits that she works on her nerves. She wants to do gymnastics, dancing, etc. The wife of the policeman referred to above "had to be doing something all the time." In two other cases the over-activity was sadly complicated by constant nagging and scolding. A woman of 32 frankly admitted, "I was going it all the time with my tongue; I could not keep still." Another patient of 59 had to be continually checked in her loquacity by her daughters, "Keep quiet, mother, you have said enough." It is not to be wondered at that in the home of the hyperthyroid woman, marital complications are not infrequent, even with a long-suffering husband.

The mood of the above patients was varied. The young woman of 27, referred to above, although irritable and with tantrums, claimed that she was quite happy. She appeared to be "keyed up"; the difference between her mood and that of the euphoric manic patient might be compared to the difference between an individual stimulated with strychnine and one who is exuberant from champagne. For a satisfactory analysis the mood must be studied in relation to the family history, and the early temperament, as well as in relation to the thyroid disorder.

As to the intellectual functions several patients mentioned difficulty in concentration and impairment of memory.

Most physicians are familiar with the general mental reaction of the myxedematous patient—the slowness, the apparent intellectual dullness, the occasional depression, the impairment

of memory. It is possible that one accepts too readily the dullness of the patient as evidence of a depressed mood.

A girl of 18 with mild hypothyroidism admitted no depression at all. A severe case of myxedema showed the gradual onset of sluggishness, day-dreaming, loss of interest: "The outside did not concern me—I was like a dead one, that's all—I had a blue spell, tears were running down like rain, I wondered why it was the way I felt." This patient when seen later in an advanced stage of myxedema said that she was not depressed, but that she was in good spirits. However, at times she would be seen crying quietly, distressed at her own condition, the seriousness of which she apparently appreciated. She was much more alert than her slow talk would indicate. She had good insight into the thought difficulty: "My thinking is not good—I don't want to think—it bothers me to think too much. There was a time when my mind was just traveling, now it is at rest." In connection with this last remark, it is interesting to note that the patient had previously been an ambitious, energetic woman, enjoying making a speech to her family circle at Thanksgiving and at Christmas time.

Another patient, a woman of forty-nine, made no reference to any depression, but emphasized the progressive loss of memory. As a waitress she had been accustomed to wait on five tables, but finally was unable to remember the order of a single person. She later kept house for her son, but was considered extremely lazy, letting her work alone until it was absolutely necessary to do it. There seemed to be little change of mood. After suitable treatment, the laziness disappeared and she felt "like a bird."

The importance of the sexual instinct in relation to mental and nervous disorders has in the past two decades received new emphasis. The analysis has been specially detailed at the psychological level, while accurate information as to the rôle played by the hormonic influence of the gonads upon the various mental functions is still far from clear. Even in thyroid and pituitary disorders the rôle played by the gonads may be far from negligible, and it is not easy to disentangle the specific contribution of the disordered action of the gonads to a pluriglandular syndrome. Such being the case, it is still more difficult to trace the relation of the hormonic influence of the gonads to mental symptoms or traits of personality, when one has to consider as well racial characteristics, individual temperament and life situation. It is interesting to study the characteristics of the Skopts, a Russian sect in which castration of the men and mutilation of the women are an essential religious rite, but the traits of character of the members of such a sect are determined by too complex factors to make such material of much value in the present discussion. Analysis of the mental traits of eunuchs and eunuchoids is also a matter of considerable difficulty. There should be a careful study of the mental disturbances in patients

in whom the gonads have been removed by operation or through trauma. I have not personally had the opportunity of studying such clinical material. The difficulty of coming to any sound conclusions even in regard to certain simple reactions is shown by the varying statements recorded in the literature. Pfister (6) calls attention to the fact that statements with regard to the continuation of sexual desire after double ovariotomy are very conflicting. In his cases the influence on the libido was very variable. The mood of about one-half of his patients after double ovariotomy was one of depression and irritability, while about one-third of the subjects felt more cheerful. The mental changes after the operation cannot be easily correlated with the variation in the hormonic situation, but are also determined by the general change in the physical well-being of the patient, by the realization of the different life-situation created by sterilization, and by the special temperament of the patient. Fischer (7) reports three cases of young men with traumatic castration. A soldier of 28, one year after the trauma, developed various attacks, first of all like asthma, later like fainting, and finally convulsive attacks in 1920; complete impotence, loss of sexual desire, irritability, suspicion, outbursts of wrath, sensitiveness to sound, periods of depression with attempts at suicide, ideas of reference. He had good insight into his change of character. A second patient, a man of 27 of cycloid temperament, is said to have developed a schizoid temperament. In a third case, the fact that the patient was blown up makes the detailed correlation of the later symptoms with the castration still more difficult. The cases utilized by Fischer indicate how unsatisfactory the available clinical material is for the solution of the problem that interests us.

With regard to the pancreas, a large amount of clinical material is available. In a small series of diabetics whom I have had the opportunity of interviewing, I have been impressed by the bright and cheerful attitude of the patients. A diabetic woman of 67, when she was asked if she were depressed, said, "Not a bit, it did not bother me; we have to get something to kill us." Another diabetic woman of 47 said, "I don't believe in feeling blue; it don't get you anywhere." Such was the general attitude of this small group of diabetics, all of whom were over 40

years of age. One patient had been rather blue and depressed, but this was not surprising in view of the fact that her husband had wanted to kill everybody and had been sent to a hospital for the insane. Another patient had been mildly depressed and unable to concentrate, but this was apparently during a period of considerable weakness.

It should not be difficult to ascertain whether in the diabetic there is a tendency to any specific disturbance of mood or thought or conduct, and whether in the psychoses incident to the disease there are features different from those met with in psychoses associated with exhaustion of other origin.

The psychiatrist sees in many patients with psychoses some evidence of endocrine anomaly; the internist sees in his patients with endocrinopathy the not infrequent development of a psychosis. The analysis of a psychosis, and the due appreciation of the various elements in the etiological constellation are matters of some difficulty; before they can be profitably undertaken we require much more light on the simpler problems discussed in this communication.

The psychiatrist looks eagerly to the physiologist and to the internist for guidance in this matter; the latter will furnish help when he renews his interest in the personality and remembers that mood, mental attitude, belief, conduct are factors in adaptation, open to objective biological study, of as much importance as the simpler metabolic machinery. The psychiatrist finds that the break-down of a patient in face of a definite environmental stress is due to the inadequate resistance of the individual, to the temperament or constitution as modified by its individual experiences. He can describe and analyze this constitution, can try with Kretschmer (8) to correlate it with physical habitus, but he cannot easily localize it or express it in the definite bio-chemical, immunological or endocrine formulae which the laboratory mind finds so satisfactory.

In his inability to specify exactly where is localized man's resistance to bereavement, thwarted career, disappointed affection, social inferiority, and to give a bio-chemical formula for it, the psychiatrist is not in a very different situation from the internist, who may be puzzled to localize the mechanism of de-

fense against the tubercle bacillus and to express it in other than complex immunological terms.

The internist steadily tries to make more specific these latter terms, to reduce them to simpler components; so the psychiatrist aims to make more precise the factors which enter into the constitutional defenses of the personality against the environmental stress and among these factors he knows that the endocrine glands play an extremely important rôle. If I have ventured as a psychiatrist to address you on a topic so complicated as that of the present communication, with so little to offer and with such slight contact with the necessary clinical material, it is in the hope that you will answer the appeal, "Come over into Macedonia, and help us."

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INTERPRETATION OF DISTURBANCES IN METABOLISM DUE TO THE GLANDS OF INTERNAL SECRETION*

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Meltzer was a convinced believer in the doctrine that most of the great advances in physiology have come from practitioners of medicine. In the field of internal secretions Addison (1860), Graves (1853), Gull (1890), Horsley (1916), Murray, Friedrich Müller and Kocher were the pioneers. That Banting, possessed of an idea, left the practice of medicine and inspired the discovery of insulin shows that the breed is not extinct. The subject matter of the internal secretions has in the course of its development become so complex that much has been written of it that is of purely imaginative character.

Many years ago Lewellys F. Barker wrote some editorials entitled "The Truth and Poetry of Uric Acid." Clinicians have stopped writing poetry about uric acid, for the field has been greatly extended. The appearance of a vast amount of poetry on the subject of endocrinology has in its turn filled the medical journals. One of the earliest themes I can recollect declared that β-granules of glycogen were carried from the livers to the heart by the blood and there in the heart, in conjunction with epinephrin, became the cause of the heart beat. I refer to this as indicative of the poetical method in science, because neither before nor since have the imaginative β-granules of glycogen been mentioned in the literature, nor did the writer of the poem vouchsafe to indicate how he had discovered them.

We all owe much to von Noorden, who came as a *Meistersinger* of old, with a melodious triangle—pancreas, thyroid, adrenal. He sang that epinephrin stimulated the thyroid, increasing protein metabolism, which it does not, and that epinephrin inhibited the pancreas and prevented the oxidation of sugar,

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which it does not, and that it caused the production of sugar from fat in the liver, which it does not. Also that the removal of the thyroid gland prevented the increase in protein metabolism in diabetes, which is actually true. Of recent date is the perfectly good theory of a very good man, Epstein (1) that trypsin destroys insulin in diabetes. I hailed this with delight, for it explained why, after giving meat to a diabetic free from urinary sugar, profound diabetes could be induced. Apparently, the meat diet increased the production of pancreatic trypsin and diabetes ensued. But alas, Collens (2), a young practitioner of medicine working in spare moments in my laboratory, has shown that the experimental evidence was inconclusive and that the results found were due to an adventitious influence upon the liver. The evidence offered is insufficient.

The heat production in a normal resting mammal is a constant, called the "basal metabolism," and in mammalia it is the same per square meter of body surface. When food is given the heat production rises above the level of the basal metabolism and this increase in the heat production is called the "specific dynamic action" of the particular food administered. During one and the same week I have read or heard discussed papers attributing the specific dynamic action to (1) thyroid; (2) adrenals; (3) sex glands; (4) hypophysis. When one considers this list one must again revert to poetry,

"Here's a pretty mess,
Here's a state of things."

I do not wish to be hypocritical, but I do wish to say just one or two things based on personal experience. In the first place, *if the dog moves,* its metabolism is not *basal metabolism.* In the second place constant confinement in a cage may reduce the basal metabolism of a dog 20 per cent. In the third place, the height of the basal metabolism depends on the plane of protein nutrition. There are all kinds of experiments on all kinds of animals which will not stand the test of a strict analysis in the light of these criteria. As far as dogs are concerned, if we know their weights, we have sufficient data to tell whether experiments reported from other laboratories are worth while or not. As far as our laboratory is concerned, we believe that we have trustworthy experimental data upon the basal metabolism

of dogs and young hogs. We feel that some good work may have been done upon cats. We are doubtful about rabbits, which are excitable little beasts, and we look askance at results obtained on chickens, pigeons, rats* and mice.

For example, Deuel's (3) work has shown conclusively that the presence or absence of vitamin B is without influence upon the basal metabolism of dogs, although Abderhalden (4), working with pigeons, found vitamin B a necessity for maintaining normal metabolism. It is easier to ascribe these latter results to an impossible technique than to a difference in the behavior of the tissue of dogs and of pigeons.

The difficulties of the subject of even simple problems related to the internal secretions are very great, as may be seen from the prolonged dispute between Cannon and Stewart, now settled by the experiments of Anrep and Daly (5), which confirm Cannon's contention that asphyxia increases the output of epinephrin from the suprarenal glands. There are excellent reviews of the literature on the subject of the respiratory metabolism as influenced by the internal secretions, such as that of Aub (6), so that I may be pardoned if today I indicate only a few salient facts.

THE THYROID

It was Friedrich Müller who first pointed out that, notwithstanding a large food intake, a patient suffering from exophthalmic goiter could not maintain his weight, and it was Magnus-Levy who carried the technically difficult respiration apparatus of Zuntz to the bedside and there proved the existence of a greatly increased metabolism in this disease. Du Bois was the first to establish accurate standards of basal metabolism for normal human beings. He differentiated between mild, severe and very severe cases of exophthalmic goiter as having metabolisms which were respectively 25, 50 and 75 per cent above that of the normal individual. This useful classification has led to the widespread employment of respiration apparatus in the clinic, though too often the value of the apparatus as an interpreter in other diseases has been ridiculously overestimated.

The discovery of thyroxin by Kendall is one of the highest significance. His writings do not reveal his methods, but the

*Asher's method with sleeping rats is reported to be reliable.

physiological effect of thyroxin is like that of the thyroid gland, relieving cretinism and myxedema. Thus, when 16 mg. of thyroxin were administered by Plummer and Boothby to a myxedematous and apparently thyroidless patient with a metabolism 30 per cent below normal, the metabolism gradually rose to a maximum and then gradually fell to the original level after a period of about six weeks. The 16 mg. of thyroxin caused a production of 16,125 calories above the quantity this patient would otherwise have produced. This is the equivalent of the heat liberated in the oxidation of 4.25 kg. of glucose. In the words of Plummer, thyroxin is "a catalyst that accelerates the formation of a quantum of potential energy in the cells of the organism." A milligram may be responsible for an increase in metabolism equal to the oxidation of 267 gm. of glucose, or 267,000 times the weight of the catalyst. Thyroxin is the most powerful agent known for inducing increased metabolism.

Kendall (7) states that the acceleration of oxidation in the animal organism by thyroxin is due to the fact that it is an active hydrogen acceptor and that the degree of stimulation is due to the oxidizing potential of this hydrogen acceptor.

In exophthalmic goiter Plummer (8) has observed that administration of iodine in the form of Lugol's solution may greatly reduce the nervous symptoms and prevent the further development of eye symptoms. He believes that two substances are active here, thyroxin and a toxic product, which latter is neutralized in the presence of iodine, which renders it innocuous. The basal metabolism falls under this procedure and the danger of operation on the thyroid is greatly reduced.

It is of great interest that in exophthalmic goiter the human machine is inefficient in the accomplishment of mechanical work. Boothby and Sandiford (9) have shown that twice the number of calories are required to accomplish a given amount of work as are normally needed.

This work of the Mayo Clinic is of a kind which, had it been produced in Germany a decade ago, would have been hailed as a triumph of German medicine. To those of us who never questioned American intellectual ability to equal the German effort it comes, not as a surprise, but as a cause for congratulation that this co-operative work of clinician, chemist and physi-

ologist should have been conducted by Americans who were born and wholly educated in this country.

It is reported from Vienna by Liebesny (10) that thymus, administered with potassium iodide, greatly reduces metabolism in hyperthyroidism. Thymus given alone is inactive, and potassium iodide alone increases the basal metabolism. These investigations might be repeated under careful control.

Recent experiments by Lauter and Jenke (11), who worked in the medical clinic of Friedrich Müller in Munich, show that, if sufficient carbohydrate be given in a case of severe exophthalmic goiter, there is no greater amount of protein metabolism than in a normal individual. Hence, thyroxin does not attack organized tissue.

An important paper by Aub, Bright and Uridil (12) shows that thyroxin acts upon the basal metabolism of cats anesthetized with urethane just as powerfully after adrenalectomy as before operation. *The adrenals are therefore not essential to the maintenance of the high metabolism induced by thyroxin.* The anesthetic prevented all muscle tremors.

THE ACTION OF EPINEPHRIN

In Addison's disease the heat production has been found to be 15 to 30 per cent below the normal. The last was a patient of Dr. L. G. Rowntree reported by Muirhead (13). Aub, Forman and Bright (14) have described how cats, forty-eight hours after the removal of the adrenal glands, manifest a reduction in metabolism of 25 per cent. Aub, Bright and Forman (15) likewise show that this fall in metabolism takes place after removing the thyroid, and hence *the thyroid has nothing to do with the reaction.* They also introduced epinephrin at the usual physiological rate of its production into thyroidectomized dogs and found an increase in metabolism. They conclude that epinephrin effects a quick, almost immediate response and thyroxin a slower one, a finding also emphasized by Boothby.

Boothby and Sandiford (16) have published an illuminating paper on the subject of calorigenic action of epinephrin. They found that the increased metabolism resulting from the administration of epinephrin in man could not be interpreted as the result of carbohydrate plethora induced by the drug. After giving 100 gm. of glucose the blood sugar doubled, and after

giving 0.5 mg. epinephrin it rose only one-third above its original level, whereas the heat production rose 9 per cent after giving glucose and 20 per cent after epinephrin. Furthermore, in a case of complete diabetes complicated with exophthalmic goiter with a basal metabolism of plus 80, epinephrin given subcutaneously increased the basal metabolism to plus 149 without any oxidation of sugar taking place. Boothby and Sandiford confirmed upon dogs the calorigenic action of epinephrin which they obtained on human beings.

Finally, they have calculated that, whereas one milligram of thyroxin induces an extra heat production of 1,008 calories, one milligram of epinephrin increases the basal metabolism only 50 calories. Calculated on the molecular basis, thyroxin is 64 times more potent than epinephrin, and epinephrin is immediate, thyroxin slow in developing its calorigenic powers.

THE PANCREAS

It would lead one very far to discuss the respiration metabolism in diabetes, and no attempt to do so will be made here. I will only mention that in certain unpublished experiments of Deuel and Chambers, performed with the aid of the respiration calorimeter of the Cornell University Medical College, it has been definitely proved that the basal metabolism of fasting dogs anesthetized with amytal may remain at a constant level for six successive hours, but when one administers insulin subcutaneously during amytal anesthesia there is often a slow but definite increase in the metabolism, persisting for at least five hours. At the end of this time the heat production may be 20 per cent or more above the normal basal level, the increased metabolism taking place at the expensee of an increased combustion of fat, as shown by the respiratory quotient. The very gradual increase in the heat production would seem to rule out any secondary influence through the adrenal. Control experiments on thyroidectomized dogs have not been carried out. The entire increase in the heat production might easily be due to abnormal conditions in the cells brought about by the low level of the blood sugar.

THE PITUITARY

The results of respiration experiments in diseases of the pituitary gland are very conflicting. Plaut (17) reports that,

whereas in diseases of the hypophysis (24 patients) and in hypophyseal obesity (32 patients) the basal metabolism rests within the normal limits, the specific dynamic action of a given diet increases the heat production by only 11 per cent, as against 28 per cent in 39 normal controls. And Liebesny (18) goes so far as to state that in hypophyseal dwarfs there is no specific dynamic action of the foodstuffs whatever.

Plaut affirms that in thyrogenous obesity both basal metabolism and specific dynamic action accord with the normal anticipation.

THE SEX GLANDS

The influence of castration upon the basal metabolism has been reported as being negligible and in other cases as tending to lower slightly the intensity of the oxidative processes. Among the latest workers in this field are Asher and Bertschi (19), who used rabbits in their experiments. They very definitely conclude, "A direct influence of the sexual glands on metabolism does not exist." Castration and ovariotomy had no influence upon the metabolism of rabbits nor had injections of testicular or ovarian extracts.

Murlin and Bailey (20) noted a slight fall in the basal metabolism of two castrated dogs, one of which had been previously thyroidectomized. This contradicts Korentschewsky (21), who states that the fall in metabolism after castration does not take place if the thyroid is first removed, and he attributes the usual post-operative fall in heat production as being due to a diminution in the amount of thyroid secretion ordinarily stimulated by the gonads.

The cause of the development of obesity in the absence of gonad secretion may be exclusively due to a decrease in the amount of muscular movement. Thus, Hoskins (22) has shown that, whereas a normal rat may run in a wheel a distance of 950 miles in one hundred days, a castrated rat may accomplish only half that distance. A hundred days after castration 16 rats ran in revolving wheels only half the distance accomplished by 16 normal controls.

I plead for simplicity of attack upon these problems. I would place the syndrome known as the "Kinetic Drive" not inside but outside the organism.

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STUDIES ON VIGOR. III. THE EFFECT OF OVARIAN EXTRACT FEEDING ON THE ACTIVITY OF OVARIECTOMIZED WHITE RATS

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Since their first use twenty-five years ago ovarian preparations for the relief of various menstrual and accompanying disorders have had much consideration by clinicians. These preparations have been of several kinds: follicular, luteal, interstitial, and of whole ovary; in various vehicles as normal saline, alkali, glycerine, or in dry form. Administration by mouth has usually been preferred and glycerine extracts have come into some degree of favor. For example, Hancher and Rogers (1) have reported recently a number of cases in which the patients showed striking improvement following the use of glycerine extract of whole pig ovary. However, the inherent limitations on clinical observation and deduction, due especially to the variable psychic factors, offer obvious difficulties in reaching dependable conclusions. Clearly, the first problem demanding solution is whether a given extract has any potency whatever. The fact that oöphorectomy in the white rat causes a sharply marked and easily recorded depression in spontaneous activity would seem to offer an unusually favorable opportunity for solving this primary problem. The fact that the data are absolutely objective, being secured automatically without human intervention, is a particularly valuable feature of such investigation in the field of the sex hormones.

In this study observations were made on eight doubly ovariectomized rats and seven litter mate controls from seven different litters. At the ages of thirty to forty-seven days the seven litters were placed in individual activity cages for matching. The cage, described elsewhere (2), consists, in brief, of a cylindrical metal drum with sides of hardware cloth fixed on a rotating axis whose revolutions are recorded by an automatic counter. In free communication with the cylinder is a small sleeping and

feeding compartment (see Fig. 1). The whole is in the main an adaptation of the apparatus originally used and described by Stewart (3). The rats remained in the cages from eighty-seven to two hundred forty-three days before ovariectomy, the average time being one hundred thirty-three days. At ages varying between forty-six and seventy-two days and averaging fifty-eight the activity took on the cyclic character described by Wang (4) and Slonaker (5). When curves of the daily activity were

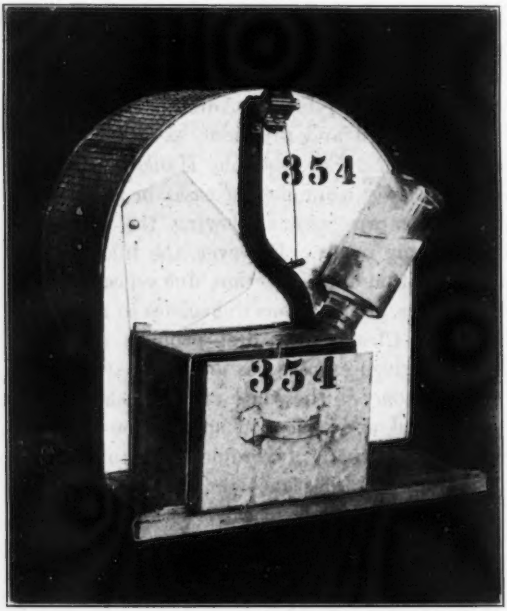

Fig. 1. Cut of recording activity cage.

plotted they showed high peaks (Fig. 2) every four or five days, corresponding to the estrus cycle as determined by the vaginal smear method described by Stockard and Papanicolaou (6) for the guinea pig and by Long and Evans (7) for the white rat. Using the microscopic findings as a check on the activity curves, our observations confirm Wang's conclusion that the animal is "most active during estrus."

After matching as to vigor, pairs of animals of as nearly equal activity and weight as possible were selected from each litter with an additional rat from one of the litters. The more active in each pair was ovariectomized. Through a median dorsal skin incision stab wounds were made over the region of each ovary and the ovary excised after ligation of the uterine horn and its accompanying vessels. The skin incision only was closed by sutures. As the white rat is known to resist infection

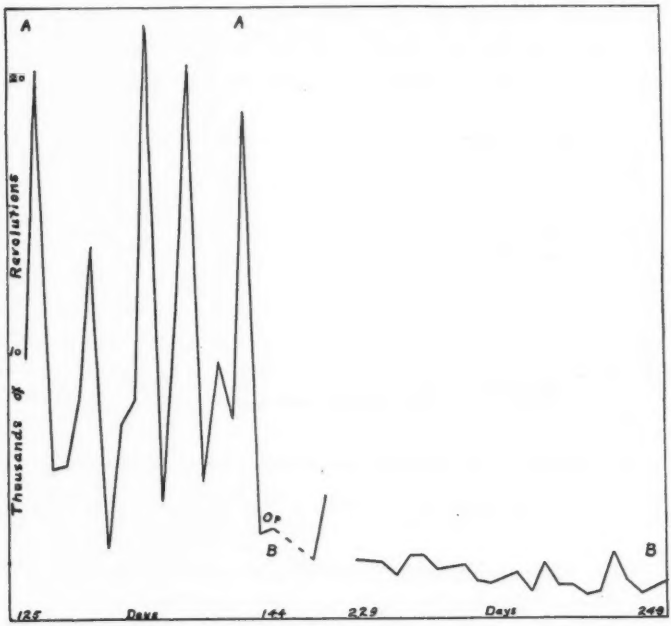

Fig. 2. Typical graph of activity of female rat; A-A before ovariectomy; B-B after ovariectomy. The horizontal axis shows the age in days, the vertical gives the number of revolutions per day in thousands.

remarkably well, only ordinary care was taken for asepsis, the skin being simply sponged with mercurochrome solution while the instruments, cotton and sutures used were subjected to a bath of 0.5 per cent lysol. Ether was employed for anesthesia. In a number of experiments in this laboratory sham operations (simple laparotomies) have been shown to have little or no effect on the activity of the animals, so that it was deemed un-

necessary to traumatize the controls. The ovariectomized animals were in most cases returned at once to the activity cages.

As shown by Wang (4) and Slonaker (5), the effect of ovariectomy is to reduce the activity to a much lower level and largely to abolish its periodicity (Fig. 2). Four of the eight castrated rats in this experiment regained their activity to some extent and showed slight evidence of periodicity for a short time, but within twenty days fell to the low level which, with the usual slight daily variations, was maintained through the remainder of the experiment. It will be seen that our experience in this respect is not in entire accord with that of Allen et

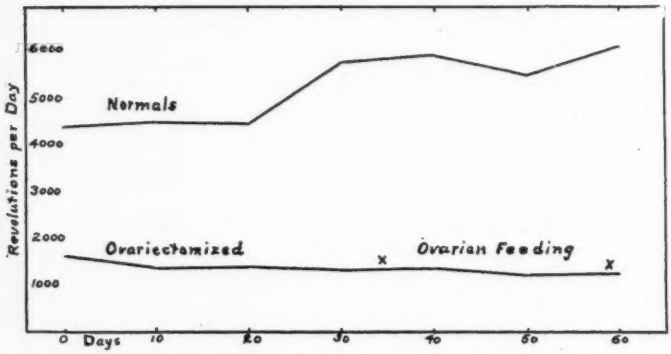

Fig. 3. Composite graphs of activity of four normal and eight ovariectomized rats before and during ovarian feeding. X-X period of feeding.

al. (8), who consider animals suitable for testing the effects of follicular extract in five days after the operation.

Hancher and Rogers (1) found glycerine extract of entire ovary most effective both in their clinical work and in experiments on guinea pigs and dogs. It was therefore decided to follow a similar method in this experiment. In preparing the ovarian extract pig ovaries were obtained from a local packing company and within an hour of removal from the animals were cleared of fat and connective tissue as far as possible by mechanical means, the follicles ruptured, the ovaries comminuted, and the whole mass ground in sand. To the mass of tissue and

fluid was then added gradually four-fifths of its volume of glycerine. This was thoroughly mixed and allowed to stand for eighteen hours, after which the liquid portion was expressed through several layers of fine gauze.

When the animals were from two-hundred-seventy to two-hundred-ninety-seven days old and the litter controls still manifesting the typical activity of estruation the feeding was begun, first on a group of four, then after a week on three others, and after a second week on the remaining one, the week interval in this case being allowed for it to attain the usual low and uniform level of activity. Twenty-five hundredths cc. of the glycerine extract was fed daily at 1 p. m. (by means of a specially graduated pipette) just after the day's run had been read. This was continued for twenty-one days, a period equivalent to four or five estrus cycles. Three of the rats were next given three successive doses of 0.5 cc. each at intervals of four hours. Three others were then given three doses of 1.0 cc. each at three and one-half hour intervals. One of this group tolerated with difficulty the entire 1.0 cc. dose, and another refused the third dose entirely, although all took 0.25 to 0.5 cc. with avidity. It should be noted that these doses were relatively enormous, the weight of the rats being approximately one three-hundredths that of adult human subjects. However, no evidence of a toxic effect was detected, except for the refusal of the largest doses by the two rats mentioned.

RESULTS

A careful comparison of the daily activity of the ovary-fed rats with that of their controls and with their respective records before feeding fails to reveal any effect from the extract whatever. The table shows, with other data, the average daily activity of each animal reckoned by ten-day periods. Fig. 3 gives a composite graph of four controls and eight castrated rats plotted from the data given in the table. Three of the controls had to be killed before the end of the experiment on account of otitis media and are omitted from the composite with view to greater exactness. The ten-day periods are indicated on the

Animal	Age in Days	A			B				C			D		
C 324	114	4413	3729	5322	4744	3949	3120	3153	2062	2582	4634	3722	3670	3322
E 332	114	11847	10266	8220	4826	4359	1549	2091	1295	867	206	222	265	117
C 353	185	8249	7070	4689	5522	5467	4652	3853	3894	6711	7262	4235	8935	7150
E 355	185	12679	8922	6036	2894	2633	1843	1343	1581	2221	1656	1656	1066	792
C 370	177	7978	11487	5100	5781	4140	4070	4408	4865	4000	4124	4311	Killed	
E 369	177	11296	9833	4078	2743	1809	1578	1491	1522	2058	2188	1262	852	525
C 381	173	3372	3979	3494	4421	3374	5194	4319	4412	4035	2974	Killed		
E 380	173	4714	7819	5298	1833	1583	1959	1286	1435	1408	789	1440	1430	1405
C 390	92	11520	10869	8122	8000	11282	6972	7702	5839	5587	5279	3214	6743	4246
E 392	92	9665	7948	9177	4051	7605	2419	1941	1626	1715	1582	1392	1194	940
C 417	111	8978	10843	11565	5935	6741	5753	5404	6660	6048	8201	9609	6934	8392
E 414	276	5480	6838	8254	4491	2645	2744	2306	*		2645	2744	2306	2290
E 416	111	7711	9110	7043	5343	7589	3754	1784	1110	937	1171	1904	1779	1910
C 426	87	10772	7667	4008	4628	5661	4567	5382	4194	4324	8832	7489	6092	5927
E 427	87	8089	9076	7568	1920	2420	2733	1312	1196	1101	1112	1033	1377	1012

The columns above give the average daily number of turns of the cage run by each animal when averaged for successive ten-day periods.
A—Gives the thirty days before ovariectomy. B—Forty days immediately following ovariectomy. C—Thirty days before the ovarian extract was fed. D—Thirty days in which the extract was fed. Control animals are designated by "C" and ovariectomized by "E" *—Feeding begun one week after ovariectomy.

horizontal axis, the average daily activity in thousands of revolutions on the vertical. The graph exhibits the same facts as the individual records, but with a smoother curve on account of the ten-day averages, instead of daily readings being utilized. As will be seen from the control graph, the feeding was done during a period of increasing activity, hence the failure of augmentation from ovarian feeding is doubly significant. The activity not having been affected, it would be expected from the known correlation between activity and estruation that the vaginal smears would prove negative, and on examination such was found to be the case.

DISCUSSION

It does not seem likely that the hormone, granting its existence, would have been destroyed by glycerine extraction, but rather that it was rendered ineffective by the digestive processes, or for other causes failed to reached the blood stream in potent form or in adequate quantity, since it has been shown by Allen and Doisy (9) that follicular fluid alone, when given subcutaneously, is able to bring about the various vaginal changes of the estrus cycle. Another possibility with preparations of entire ovary, as indicated by the work of Dixon and Marshall (10), is that the luteal incretion to some extent or in some conditions represses follicular activity or perhaps neutralizes the follicular principle sufficiently to prevent the effect characteristic of liquor folliculi collected from isolated follicles.

As bearing on the adequacy of the technic employed to demonstrate the efficacy of ovarian hormones, it may be stated that Wang (4) showed marked restoration of activity following successful ovarian grafts.

SUMMARY

In an experiment with eight doubly ovariectomized and seven litter control white rats, the daily feeding of glycerine extract of whole pig ovary for a period of three weeks had no effect on the voluntary activity of the ovariectomized animals. Thrice daily feeding of large doses was likewise ineffective. In view of the proved adequacy of the method used to detect the

influence of ovarian hormone these experiments cast further doubt on the efficacy of ovarian preparations administered by mouth.

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AN UNUSUAL CASE OF HETEROGENITALISM*

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H. W., a schoolboy 16 years of age, born in New York City of Jewish parents, was brought to the Neurological Institute, December 30, 1924, because of backwardness in school and childishness of behavior.

Family History. The mother and father were born in Poland and came to the United States as young adults. They are both living and well. One brother, born of the second pregnancy, died of convulsions at six months. The patient is the youngest child. There were no miscarriages. There is no history of goitre, diabetes, dwarfism, gigantism, migraine, epilepsy, nor insanity in the family.

Developmental History. The labor was at full term, but difficult owing to the presence of fibroid tumors of the uterus. The delivery was instrumental. The child showed no evidence of injury and respiration started normally. There was no evidence of the presence of a dead twin.

The patient was a sickly baby and was subject to frequent attacks of colic and vomiting, which continued through his second year. There was a single convulsion at six months. The patient sat up, cut his teeth, walked and talked at the proper ages. He entered the public school at the age of six.

Patient's History. The patient has had the usual childhood diseases. He had grippe at 12 years. There were no serious illnesses. There is no history of bed wetting, nose bleeding, headache, hay fever, eczema, urticaria nor asthma. The patient broke his left arm at 6 years, which healed satisfactorily. There were no operations.

Present Illness. The first symptom called to the parents' attention was backwardness in school. He has had to repeat every grade and is now in grade 6-B.

It is only within the past two years that the parents have regarded his behavior as abnormal. The patient prefers to play with children much younger than himself, is inattentive, easily distracted and incapable of taking directions. He becomes nervous, confused and loses his temper when he does not comprehend what is wanted of him. He is emotionally unstable, timid, and apprehensive. These symptoms are becoming more pronounced.

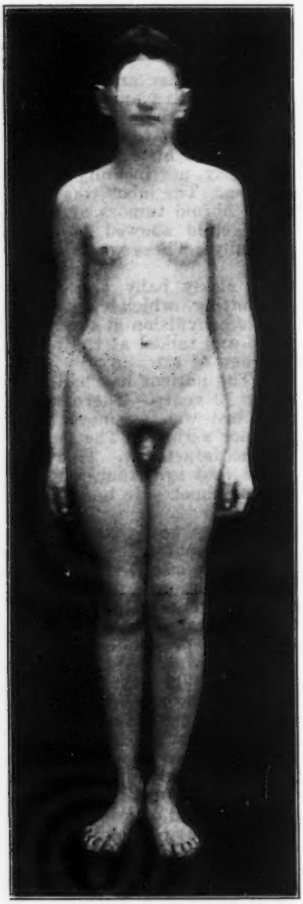
No physical abnormality was noted by the parents before bringing the patient to the clinic. When the abnormal breast development was called to their attention the parents seemed quite surprised and stated that this condition did not exist the previous summer. This statement seems to be born out by the patient as he asked for a written permission to excuse him from gymnasium as the other boys had recently taken to teasing him and calling him a girl.

Habits. The patient's appetite is good; he sleeps well; his bowels are regular. He is not over fond of sweets and he has no polydipsia nor polyuria. The parents have never seen any evidence of masturbation nor pollutions.

Endocrine Status. The height is 159.5 cm.; the weight 117¾ lbs.

*Hetereogenitalism is submitted as a better term than pseudo-hermaphroditism.

(53.5 kgms.) stripped. The head is moderately microcephalic; there is moderate lumbar lordosis; no prognathism; no maxillary torus; feminine contour; broad pelvis. There is hyperextension of all joints and a moderate degree of flat foot. The size of the hands and feet is not disproportionate. The facial type is not characteristic. Growth



has been rapid within the past year, but no measurements were made prior to the present examination. The present measurements are as follows: Torso-leg ratio, 40.5-85 cm.; spread of arms, 159 cm.; Bust (mid-expansion), 79.5 cm.; shoulders (bisacromial diameter), 37.5 cm.; waist, 69.5 cm.; hips at greater trochanters, 89.5 cm.; interpupillary distance, 58 mm.

Skin. The skin is fine, smooth and moist. The nails are bitten off short. There is no eruption. There is a faint pink line on stroking the skin of the chest and abdomen.

Teeth. The teeth are close together, but not crowded. The central invisors are broad, rounded and imperfectly enameled. The lateral incisors are rather small. The canines are well differentiated. The second bicuspids and third molars have not descended.

Hair. The hair of the head is black, thick, coarse and curly. The temporal hair almost reaches the outer edge of the eyebrow on each side. There is no nasal brow. There is beginning axillary and pubic hair and the lanugo on the upper lip and back is darkened.

Muscle. The muscular development is not abnormal. There is no increased muscular irritability nor myoidema. There are no muscle or tendon contractures and no locallized weakness, atrophy or hypertrophy.

Glands. The tonsils are large and the cervical glands are palpable. The axillary and inguinal glands are not enlarged. The tongue papillae are not enlarged. The thyroid is barely palpable.

The breasts are large, of the adolescent female type, and contain readily palpable gland tissue. The nipples are rudimentary.

Pigment. There are no abnormal pigment deposits on the skin, teeth or mucus membrances.

Genito-urinary Organs. The penis is well formed and of about normal size. The prepuce has been circumcised. There is a scrotal fold surrounding the base of the penis. The testes are descended, but are small and soft. Rectal examination revealed a normal prostate. No abnormal organs could be palpated. The patient claims to have occasional erections, although the bulbocavernosus reflex could not be demonstrated. There is no history of pollutions.

Cardiovascular System. The pulse is 84 and the blood pressure 128-60. The blood vessels are rather small.

The general physical and neurological examinations disclosed nothing noteworthy.

Laboratory Examinations. The blood count is as follows: R. B. C., 4,200,000; hemoglobin, 80%; W. B. C., 6,500; polymorphonuclears, 62%; small lymphocytes, 32%; large lymphocytes, 4%; eosinophiles, 2%. The coagulation time (Biffi-Brooks) is 13 min. The blood sugar is 0.09%. The carbon dioxide combining power is 51%. Blood Wassermann examination is negative. Upon analysis the urine is found normal.

X-ray Report. Examination of the skull shows the calvarium to be even in outline but irregular in thickness. The circulatory channels are normally visible. There is no evidence of increased intracranial pressure. The sella is small, but well rounded and wide open. The basal angle is normal. Essentially the examination is not remarkable except for the questionably small sella.

Examination of the thorax shows the trachea to be in the midline. The aortic arch is clearly defined. There are no abnormal shadows in the superior mediastinum.

The intelligence quotient as measured by the Terman test is 0.55 which places the patient in the moron group.

SUMMARY

A boy of 16 years is described showing mental and behavioristic retardation associated with a feminine contour and breast development of the adolescent female type. The penis is well developed and the testes descended, though soft. No abnormality could be discerned in the formation of the generative system with the exception of the soft testes. Rectal examination revealed nothing abnormal.

THE EFFECT OF SINGLE DOSES OF THYROID GLAND ON FOWLS

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In a former article* were published the results of three years of observation on the effects of feeding fowls thyroid gland. The usual symptoms of hyperthyroidism, such as increased excitability, polydipsia, polyphagia, tremors and diarrhea, were recorded. Four peculiar phenomena hitherto unnoticed were described: (1) Premature "experimental" moulting; (2) Replacement of the former colored feathers by depigmented white feathers; (3) From prolonged toxic dosing neuropathological symptoms marked by depression alternating with flashes of excitability, followed by cessation of co-ordinated movements; (4) From further administrations of large doses, death preceded by characteristic tremors.

In all these experiments daily, systematic administration of thyroid or preparations of the gland were employed. This method required much time and trouble, and at the periods of acute poisoning the fowls had to be fed artificially twice a day. Attempts at simplification were therefore made.

Previous investigations had demonstrated that to obtain "qualitative reactions" one administration of thyroid gland was sufficient. These experiments also showed the occurrence of a certain cumulative action of the thyroid; fowls are very resistant to thyroid treatment and can at one administration absorb very large doses, larger than the sum total of daily lesser applications.

The present investigations have been conducted for the following purposes: (1) to arrive at a simpler way of attaining the symptoms of hyperthyroidism, as already described; (2) to get a direct proof of the phenomena of cumulative action of the hormone of the thyroid gland; (3) to discover what single

*The effect of feeding fowls on thyroid gland. Zavadowsky, B.: This Journal, 1925, 9, 125.

dose will be fatal for fowls, and to study the accompanying neuropathological phenomena.

Among other possible simpler methods grafting of the gland was tried. For this purpose a mongrel black hen, utilized in previous studies as a control bird, was used. This hen had in the interim been experimented on with inorganic iodine. These experiments will be published in a subsequent article. This fowl on July 31, 1923, had its feathers plucked away under the wing, and there were grafted under the skin five dogs' thyroid glands.

Aug. 5. The skin on the spot engrafted became inflamed.
Aug. 7. The hen was in a typical depressed or excited condition and would not allow handling; the feathers were firm.
Aug. 17. The feathers were still firm, but tufts of white feathers appeared at the site of the graft.
Aug. 20. The feathers on the spot operated on were grown to full length, and had large white tips. There was no moulting.

This hen in the previous control experiments had had the feathers under the wing or the legs repeatedly plucked, and on each occasion there had grown pure black feathers; therefore the partial depigmentation in this case must be attributable solely to the action of the glands implanted. In this case all the previous observations were repeated, namely, that *pigmentary phenomena require very much less thyroid than those of moulting;* thus, in this experiment, despite the summer season when normal moulting might have been expected, the grafting caused whitening of only the new growth of feathers.

Further experiments were carried out using single doses of desiccated thyroid gland. For this purpose material from horses was prepared in advance during the winter. The glands were cut into fine shreds and desiccated in thermostats at a temperature of 40-50° C. These experiments showed convincingly the correctness of the former hypotheses. The phenomena of discoloration above mentioned were reproduced, and were even more pronounced than before. However, the resistance of the birds to additional administration of thyroid gland was exhibited to an unexpected extent.

Experiment 1. A spotted hen; weight 1725 gm.
July 18, 1923. Fifteen grams of desiccated thyroid gland was given.
July 25. The feathers were dropping profusely.
July 27. The weight was 1400 gm. The hen was very naked and highly excitable.
July 31. It was literally stripped of all its plumage except for

a few feathers on the tail and the down. All the rest of the body was covered with little stumps of growing feathers.

Aug. 7. The stumps of the young feathers were beginning to stand out; but the newly developing crest, instead of the previous straw color, was pure white, with weakened outlines compared with the former black.

Experiment 2. A yellow hen; weight 1660 gm.

July 24, 1923. Twenty-five grams was administered.

July 27. The weight was 1650 gm. Moulting was marked.

July 31. Many feathers were lost.

Aug. 2. It had almost caught up with the spotted hen.

Aug. 5. It was more naked than the spotted hen.

Aug. 7. The weight was 1415 gm. The hen was almost completely naked and the remaining feathers were very weak. On each wing was one straw-colored feather. On the left wing there were also three covering feathers; on the occiput were 11 feathers; on the back, 2; near the tail, 5; on the belly, 10. The remainder of the body was covered with stumps of newly-grown feathers. (See Fig. 1.)

Fig. 1. A yellow hen in the state of moulting (Experiment 1).

Aug. 14. The feathers were growing rapidly, and had white spots on them.

Still larger doses were next administered and the phenomena of depigmentation under similar conditions on pure black fowls were verified.

Experiment 3. A pure black hen; weight 1632 gm.

July 31. Fifty grams of desiccated thyroid gland was administered.

Aug. 1. The hen was alive but somewhat sickly and depressed.

Aug. 2. It was depressed, but alive and ate well.

Aug. 5. The feathers were loose. The bird was in a very nervous condition.

Aug. 7. The condition of depressed excitement continued.

Fig. 2. A pure black hen in the state of moulting (Experiment 3).

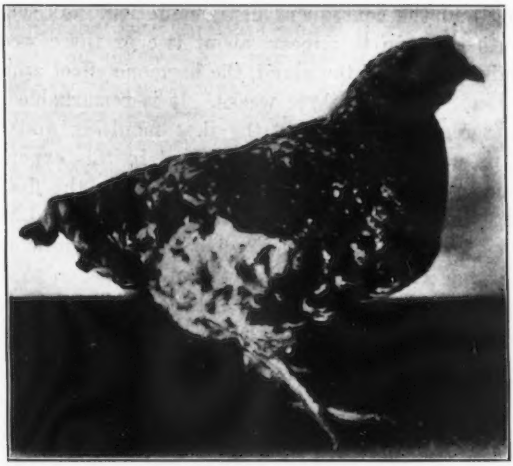

Fig. 3. Same hen as in Fig. 2 with renewed feathers.

Aug. 8. The plumage scarcely held; fresh stumps were already discernible.

Aug. 14. The hen was almost entirely naked, and in an excited condition.

Aug. 16. It was very naked, but less so than the yellow hen. Extensive growth of white feathers was noted. (See Fig. 2.)

Aug. 21. There was very marked moulting.

Sept. 20. The new plumage was complete and there were almost as many white as black feathers. The weight was 1547 gm. (See Fig. 3.)

Experiment 4. Minorca No. 15; pure black; pure bred; weight 2350 gm.

Aug. 7. Twenty-five grams was administered.

Aug. 10. The feathers were already moulting.

Aug. 14. There was marked moulting; the bird showed both depression and excitement of marked degree.

Aug. 16. It was naked, but less so than No. 3.

Aug. 28. The hen was still not quite naked; growth of many white feathers was observed.

Sept. 1. There was a plentiful covering of white feathers.

Additional administration of from 15 to 50 gm. of desiccated thyroid gland was thus proved convincingly to be sufficient to produce fundamental symptoms of the phenomena of moulting and the consequent depigmentation. As soon as the new feathers begin to appear, about two or three weeks after the administration of the gland, the hormone effect appears and lasts for not less than three weeks. It is remarkable also that the same regular periods of the first moulting and the first growth of white feathers were observed in this experiment as in the one previously reported. As stated in the first article, moulting starts in from seven to thirteen days, and the white feathers appear in from twenty-five to twenty-nine days, depending upon the dosage. The spotted hen began to moult on the seventh day; the yellow hen between the third and sixth; the black in Experiment 3 on the sixth; and the Minorca on the seventh. Weakening of the roots of the feathers rather than the natural course of moulting accounts for the reaction on the third day in the case of the yellow hen. White feathers appeared on the spotted hen on the twenty-second day; the yellow hen on the twenty-first; the black hen of Experiment 3 on the twenty-seventh; and the Minorca on the twenty-first day.

Thus in both cases there was a tendency towards acceleration of the phenomena; this agrees with previous observations that stronger doses of the hormone hasten the reaction. This problem of the effect of increased doses on the degree of the reaction was tested in accordance with the new method. To this end, and also to discover the minimum dose which would produce a noticeable result, the following experiment was devised:

Experiment 5. Black hen.

Aug. 17. Five grams of desiccated gland was administered.

Aug. 23. Some feathers began dropping; in general moulting was not marked, but feathers could be pulled out more easily than usual.

Aug. 28. Moulting was noticeable, but only in small amounts. The plumage was thinner and ragged. The weight was 1729 gm. Twenty-five more grams was administered.

Sept. 4. The hen became markedly naked.

Sept. 20. There were many white feathers.

This experiment confirms the fact that a certain relation exists between the amount of thyroid substance administered and denudation and depigmentation. This was manifested not only by the slight moulting of the black hen (Experiment 5), but also by the long duration of the period of ineffectiveness in some earlier experiments with smaller frequent doses, when the first moulting was on the eleventh day and the growth of white feathers on the twenty-seventh, instead of the shorter periods when the maximum doses were given. A dose of 5 gm, may be considered as approximately the minimum additional dose sufficient to produce a noticeable reaction in the plumage and in the organism of the bird.

Experiment 6

In order to determine this question finally two chickens, three to four months old, weighing respectively 1035 and 1040 gm. each, were given 2 gm. of desiccated gland.

Aug. 28. Six chickens weighing from 389 to 575 gm, were given 5 gm. each.

Sept. 7 and 11. The two first under observation showed very slight moulting and only a few of the six others showed signs of moulting.

Sept. 17. It seems sufficiently evident that the minimum dose of thyroid gland sufficient to cause slight but noticeable symptoms of moulting in fowls weighing 1 kg. may be estimated at 1-2 gm. These figures apply to the autumn season and vary in accordance

with individual peculiarities and the species of fowl. Further research is needed.

The fowls were found to be astonishingly resistant to large doses of thyroid. Possibly there are no limits to this resistance. Doses of 25 and 50 gm. of desiccated gland seem to be the most practicable for the experimenter who has to thrust into the bird's beak lumps of the gland. Even with the maximum doses the fowls betrayed no signs of that nervous pathological depression, a condition approaching lethal poisoning, such as was described in the previous article. Therefore, particular interest was felt in verifying the cumulative effect of the poison.

Experiment 7. A small black hen; weight 1400 gm.

July 31-Aug. 4. Four grams of desiccated gland was administered daily.

Aug. 4. There was noticeable weakening of the feathers; they fell out at a touch of the hand.

Aug. 6. The hen was found dead, in the attitude typical of thyroid poisoning, the feathers scarcely holding to the body.

In six days this hen was fed 24 gm. of the gland, while doses of 25 gm. were taken by fowls of the same weight without any sign of marked poisoning, thus demonstrating the cumulative effect of the gland. Further research is needed, however, as to the characteristics and operation of these phenomena. It is probable that with limited administrations the bird's organism manages to discharge a considerable part of the substance before it is absorbed into the blood; while with smaller but systematic doses the whole of the hormone introduced is assimilated. It is almost impossible under the conditions of our autumn experiments to administer a lethal dose to fowls. The method of additional doses facilitates the observation of all the phenomena hitherto described and renders them extraordinarily effective. It enables the experimenter to strip the fowl in a fortnight and also to get in the third week an abundant growth of white feathers without the accompanying symptoms of acute poisoning or risk of fatal termination. A further advantage in this method is that there is a constant change of plumage, a complete renewal. This led to the discovery of the fact that *the new plumage which makes its appearance after the experimental moulting is apparently much softer than the old ordinary plumage.* This has not been verified, however, by morphologic and microscopic analysis of the nature of this newly grown plumage.

The new method has made it possible to study one other

heretofore unanalyzed phenomenon. In the first article the fact that it was easier to get an effective moulting in autumn than in spring was mentioned. The extent to which this phenomenon is connected with the influence of the sexual hormone, the action of which is opposite to that of the thyroid, was studied. It has now been convincingly demonstrated that the *growth of the feathers* plays the leading part; *the young feathers that have grown just after the experimental moulting are very much less liable to be moulted a second time.*

Experiment 8. A spotted hen, which had moulted again after a dose of 15 gm. on July 18

Aug. 14. Twenty-three grams of thyroid gland was administered.

Aug. 21. A test proved the firmness of the feathers. The weight was 1325 gm.

Aug. 23. Thirty grams was administered.

Aug. 28. The plumage was still quite firm. Twenty-five grams was administered.

Sept. 4. The feathers were slightly weaker on the nape, but, generally speaking, there was nothing resembling moulting. The fowl seemed depressed.

Sept. 9. There was slight moulting of feathers on the nape. The depression continued up to the time of writing, Sept. 15.

Experiment 9. A yellow hen which had moulted after administration of 25 gm. on July 24

Aug. 23. Thirty grams of desiccated gland was administered.

Aug. 28. The feathers were perfectly firm. The plumage was decidedly softer and smoother than on the other fowls.

Sept. 4, 7, 14. The feathers were firm.

Experiment 10

The experiment was conducted on a hen to which doses of 1 gm. had been regularly administered from Aug. 2 to Aug. 16, resulting in the production of partial moulting accompanied by a change from black to white plumage.

Aug. 17. Twenty-five grams of gland was administered.

Aug. 23. The bird strayed about, but the white feathers that had appeared after the preceding doses were retained.

This shows that the degree and nature of moulting in fowls depend largely on the age of the feathers. That such feathers are not absolutely immune, however, to an experimental second moulting was ascertained on the spotted hen after a third application of a strong dose of thyroid. In this, as in its influence on the other functions of the organism, the thyroid hormone appears to be a typical catalyser.

SUMMARY

1. One strong dose of thyroid gland is sufficient to induce specific phenomena of moulting and depigmentation on fowls as described in a previous article.

2. Fowls exhibit extraordinary ability to withstand large single doses; even 50 gm. of thyroid gland at a single dose fails to educe those symptoms of acute poisoning previously noticed, such as neuropathologic fits, ending in death with tremors and convulsions.

3. The fact of cumulative action of the hormone of thyroid gland is confirmed. Fowls can endure at one application much stronger doses than in constant daily smaller administrations.

4. The periods previously given for the beginning of moulting and the appearance of white feathers have been corroborated with the reservation, however, that the rapidity and extent of the reaction depend on the size of the dose, maximum doses inducing moulting on the sixth day and the first appearance of white feathers on the seventeenth to the twenty-first day. When smaller doses are administered the periods are respectivly eleven to thirteen days and twenty-nine days.

5. The minimum dose of thyroid gland which will induce a noticeable reaction in moulting and depigmentation on fowls was found to be 1-2 gm. desiccated gland per kilo from June to October.

6. The new growth of feathers after experimental moulting can be subjected to a second moulting in the same way only with great difficulty. The growth of the plumage, therefore, is the essential factor in determining the degree of the reaction to the thyroid gland substance.

7. The new method of single doses enables the experimenter within a fortnight to deplume any fowl and in four weeks to be sure of an appearance of white feathers.

8. The new plumage that grows after experimental moulting is markedly softer than the normal.

9. The fact that the growth of the new feathers comes about in three weeks after thyroid feeding proves that the action of each administration continues not less than three weeks after

the introduction of the hormone into the organism. This fact corresponds with the characteristics of thyroxin stated by Kendall*, in men and mammals. The action of thyroxin on fowls will probably be investigated at a later date.

10. Grafting dog thyroid glands in fowls produced whitening of the feathers at the site of the operation, but no moulting. This proves that the thyroid gland acts more sensitively to produce depigmentation than moulting—a fact already noted at the outset of the former experiments.

*The physiologic action of thyroxin. This Journal, 1919, 3, 156-163.

Editorial

PARATHYRIN (COLLIP)

Organotherapy since several years has been bombarded with ridicule and censure. In the enthusiasm for applying this novel therapy endocrine extracts have been prescribed in innumerable conditions where the theoretical clinical indications for their usage have been of whimsical, flimsy texture. Rebuke for such hazy therapeutics has been warranted. More lamentable, however, was the failure to achieve improvement in endocrine deficiencies where the fundamental indications for glandular therapy were positive and sound. It is but a short time since pancreatic therapy for diabetes mellitus was utterly futile. How different now with insulin. It is no simple matter to produce potent extracts. Hormones are delicate structures, easy to destroy in the process of manufacture and harmed sometimes by intestinal juices.

It is therefore a matter of congratulation that Professor Collip of the University of Alberta, Canada (who it will be remembered contributed to the isolation of insulin), has added another potent extract to the field of organotherapy. Whether or no his extract contains a perfect parathyroid hormone or all the active principles, if there be more than one, is impossible to state at this time, but most emphatically *it does contain a something that does something.* In other words, injection of this extract exercises a profound influence on the blood calcium content, just as insulin affects the blood sugar, only in an opposite direction. It raises the blood calcium, whereas insulin lowers the blood sugar. A further proof of its potency is evidenced by the alarming possibilities from overdosage. Collip has produced hypercalcemia experimentally in dogs, with fatal result and such complete clotting of the blood that at times no serum could be obtained for blood calcium determinations.

It is earnestly to be hoped that clinical experimentation with this potent parathyroid extract will shed some light on the mys-

teries of parathyroid function. Despite the prodigious amount of investigation that has concerned itself with these tiny glandules, much remains to be explained, confirmed or disproved. We know that tetany results from clinical or experimental removal of these glands. We know that the blood calcium sinks to a low level under these circumstances. We know that Collip's parathyrin will raise the blood calcium promptly and thus relieve the tetany; not only has this been confirmed in animals experimentally, but already in a few cases of human tetany following thyroidectomy.

Is tetany the only clinical syndrome that follows parathyroid deficiency? On the face of it, this would seem unlikely. It is to be remembered that juvenile cataract has complicated juvenile tetany and been reproduced in animals following parathyroidectomy. Curious punctate enamel defects in the teeth have also been noted clinically and produced experimentally. Further clinical experimentation will probably follow two directions, a trial of parathyrin in diseases supposedly involved with a disordered calcium metabolism (such as rickets, osteomalacia, possibly certain types of delayed coagulation, chronic ulcers, urticaria, etc.) and a trial in diseases where acute or chronic spasm plays a prominent role (epilepsy, asthma, hay fever, vasomotor rhinitis, angioneurotic edema, spasmophilia, hypertension, etc.).

At first thought, it would seem fantastic to assemble such a weird company under one roof, and it is unlikely that many of them will be benefited by parathyroid therapy. However, we must admit that we know very little concerning the etiology of any of them, and a therapeutic trial of a potent extract has some justification. At least it may result in squelching the rumors of parathyroid participation. And again it may be found that parathyrin possesses pharmacodynamic powers like adrenalin and pituitrin, of benefit in conditions quite unrelated to parathyroid function.

However it may turn out, the door of opportunity is open. Much or little may come of it. Let us hope that the clinical fishing expedition that will inevitably result will be conducted soberly and judiciously with accuracy and discrimination. And

meanwhile it will be prudent to beware of premature announcements.

It is gratifying that the same firm that pioneered so well with insulin has undertaken the manufacture of this new parathyroid extract. H. L.

Abstract Department

The increase of adrenin action by amino acids (Weiterer Beitrag zur Kenntnis der Wirkungssteigerung von Adrenalin durch Aminosäuren). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **206**, 154-161.

Aliphatic, homo- and hetero-cyclic amino acids (glycine, alanine, glutamic acid, d- and l-tyrosine, di-iodotyrosine, tryptophane, and histidine) in concentrations of 1:25,000 or less, increase the action of adrenin on the surviving large intestine of the guinea-pig. Pyrrolidonecarboxylic acid, the anhydride of glutamic acid, is without action.—A. T. C.

Oxygen consumption in the adrenals (Ueber den Sauerstoffverbrauch in den Nebennieren). Broening (A.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 571-577.

Electrical stimulation of the splanchnic nerve increases oxygen consumption in the adrenals. Since during this stimulation the adrenin content diminishes, the oxygen consumption can be taken as measure of the intensity of the work of the adrenals. Injection of small doses of **thyroid** extract produces increase of oxygen consumption. Larger doses decrease it. It is decreased by large or small injctions of **pancreas** extract. Thyroid extirpation has no definite effect on this oxygen consumption (perhaps a slight decrease). Since adrenin secretion is not affected by thyroid or pancreas injection, the authors conclude that the thyroid and pancreas affect the cortex particularly.—A. T. C.

An endocrine factor in the chemical control of body temperature. Cannon (W. B.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 162-165.

A number of observers have shown that secretion from the adrenal medulla is capable of influencing the rate of metabolism in the body, thus accelerating oxidative processes. Employing the denervated heart in animals surviving and living normally, it was found that the organ is influenced only by temperature changes and by agents brought to it in the blood stream, especially adrenin, to which it is extremely sensitive. Animals thus prepared showed accelerations of heart-rate varying from 12 to 43% when taken to a cold room, from 34 to 43% when placed in an ice box, of 43% when held in the lap and exposed to the cold draught of an open window,

and between 27 and 64% when cold water was introduced into the stomach. If the adrenal glands were rendered inactive the effects did not occur. In cats with intact adrenals an injection of a suspension of dead typhoid bacilli produced fever having a characteristic course, with erection of the hairs and shivering during the maximum height of temperature. If the adrenal glands were rendered inactive by the removal of one and denervation of the other, injection of dead typhoid bacilli caused only a slow rise which in some instances was very slight. The author suggests that the response of the adrenal medulla during toxic fever is serviceable to the organism.—I. B.

A case of virilism associated with a suprarenal tumour. Holmes (G.), Quart. J. Med. (Oxford), 1925, **70**, 143-152.

A case is recorded of a young woman in whom a large, slowly growing tumor of the right suprarenal body was associated with changes in the sexual organs, disturbances of the sexual functions, alteration in the secondary sexual characters, and psychical changes, all of which symptoms disappeared within a relatively short time after the removal of the tumor and left the patient again an apparently normal woman. This subject had been under observation for 11 years, two previously to operation and nine since. Many similar cases from the literature are cited by the author, and additional clinical evidence is put forward to show that disease of the suprarenal cortex, and especially such forms as increase its functional elements, can influence the development or state of the sexual system. The author considers that the cases recorded, and especially those in which, after the removal of the tumor, the symptoms disappeared, afford evidence that must now be regarded as conclusive that an internal secretion derived from the cortex of the suprarenal bodies, when in excess, tends in women to diminish the female and increase the male primary and secondary sexual characters. He also suggests that there is abundant evidence to show not merely that active growth and development, in abnormal as well as in normal circumstances, of certain organs of the body, and especially the sexual organs and related systems, are dependent on internal secretions, but also that the growth when attained requires the continuous influence of these secretions and in their absence may regress.

—Med. Sc., **12**, 28.

Two cases of mytilism with anaphylactic shock treated with adrenalin injection. Henrichsen (S. L.), Ugesk. f. Læger (Copenhagen), 1923, **85**, 743-745.

In two cases of mussel poisoning with severe anaphylactic phenomena the author procured strikingly good effects from adrenalin injections.—K. H. K.

Effect of epinephrin by oral administration. Menninger (W. C.), J. Am. M. Ass. (Chicago), 1925, **84**, 1101-1102.

This study is based on a series of observations on the administration of epinephrin by mouth in various types of **hyperthyroid** cases. To date, a series of fourteen observations has been made on nine patients. Of this group, three have given a very definite and in one case a marked reaction, and two others have given slight reactions. Of the three cases in which the reaction was marked, the blood pressure rose (systolic) 30 mm. in one case, 50 mm. in the second and 110 mm. in the third. The pulse remained practically constant in the first two, but increased 52 beats a minute in the third. In all three cases, epigastric and substernal pain and nausea occurred. Vomiting, sweating and increased tremor occurred in two cases. In the two cases giving slight reactions, the blood pressure (systolic) rose in one case 12 mm. with a pulse increase of 20, and 18 mm. in the second with a pulse increase of 10. In both cases there was epigastric "burning" and distress. These reactions were slight and might be disregarded, excepting that control observations with smaller doses on the same patients produced no objective or subjective effects. At present, conservatively, the only conclusion to be made is that epinephrin may produce marked systemic effect on the circulation in some cases of hyperthyroidism when administered by mouth, the effect resulting from absorption through the gastro-intestinal canal and not from the mouth or throat.—A. M. A.

Studies in Addison's disease. Rowntree (L. G.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 426-450.

A summary of the results of treatment of 47 cases of Addison's disease in the Mayo Clinic since 1912, representing approximately one in every 6600 patients seen. The prognosis in these patients is extremely grave. Irrespective of the amount and intensity of the treatment, approximately two-thirds of the cases are fatal within a year. Treatment consists essentially of forced substitution organotherapy. At best, therapy can only combat functional insufficiency of the suprarenals. The Muirhead treatment should be given a fair trial in every case of Addison's disease with due respect for individual tolerance. Supplementary measures to combat the associated symptoms and underlying pathological process should likewise be instituted.—I. B.

Studies in adrenal insufficiency. Stewart (G. N.) & Rogoff (J. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 394-397.

The adrenals were removed in 36 dogs at 2 operations. All the animals died after varying intervals. Seven received intravenous injections of Ringer's solution with dextrose. Two of these lived more than 30 days after the removal of the second adrenal,

while 15 days was the longest that any untreated dog survived. Refusal of food, then vomiting and diarrhea, with blood and bile in the stools and vomitus are the symptoms shown. Just before death there may be weakness of the hind quarters. Autopsy shows congestion with hemorrhage of the mucosa of the intestinal canal below the esophagus.—J. C. D.

Basal metabolism in adiposity. Folkmar (E. O.), Ugesk. f. Læger (Copenhagen), 1924, **86**, 762-766.

The author made 300 basal metabolic determinations on 21 patients with adiposity. He considers that making merely a few examinations in each patient fails to give a reliable indication of the true basal metabolism since after continued examinations the basal metabolism in all the patients diminished 10-20%. The control subjects treated in the same manner never differed from Benedict's figures more than 5%. The patients observed did not present other signs of endocrine disease.—K. H. K.

The endocrine element in arthritis. Thompson (H. K.), Boston M. & S. J., 1925, **192**, 658-664.

In several cases of chronic arthritis there was evidence also of abnormal function of the **thyroid.** The connection between joint disease and other glands of internal secretion is not clear.—J. C. D.

The influence of the ovary on pituitary secretion. A probable factor in parturition. Dixon (W. E.) & Marshall (F. H. A.), J. Physiol. (Lond.), 1924, **59**, 276-288.

Ovarian secretion (rabbit, sow) does not cause parturition by direct action on the uterine muscle; in the absence of functional corpora lutea ovarian secretion has a specific stimulating effect in promoting pituitary secretion, which has a definite specific action upon the uterine muscle; in the presence of fully formed and functional corpora lutea ovarian secretion has no such effect because the corpora lutea inhibit the ovarian secretion; but with the involution of the corpora lutea at the close of pregnancy the stimulating effect of the ovarian secretion upon the pituitary body is reestablished, and in this way ovarian secretion, through the intermediation of the pituitary, becomes an important factor in causing labor.—Physiol. Abst., **10**, 47.

A critical study of endocrine therapy in gonad failure in the male. Lawrence (C.), Boston M. & S. J., 1925, **192**, 480-482.

The transplantation of human testicular tissue may be indicated in certain eunuchoid conditions and in castration. There is no satisfactory evidence that any of the preparations now available for either oral or intravenous administration has any therapeutic

value. The author bases his conclusion on a review of the literature.—J. C. D.

The objective determination of gonad failure in the male. Rowe (A. W.), Boston M. & S. J., 1925, **192,** 477-478.

Seven hundred cases of supposed endocrine dysfunction were studied. No satisfactory tests for gonad failure were found, since even loss of the testicle may produce very little effect on body activity and function.—J. C. D.

Diabetes from lesions in the tuber cinereum (Diabéte sucré par lésion nerveuse). Camus (J.), Gournay (J. J.) & Le Grand (A.), Presse méd. (Par.), 1925, **33,** 249-252.

Camus, Gournay and Le Grand induced experimental lesions in the region of the tuber cinereum in rabbits by introducing fine capillary glass tubes filled with a fatty acid. Glycosuria occurred in 9 rabbits out of 23, and persisted from one to several weeks. The maximal amount of sugar in the urine was 6.4 gm. percent. Microscopic examination showed injury of the tuber cinereum in the 9 positive cases, while in the 14 negative cases the lesion was located elsewhere. The microscopic findings in 8 positive cases demonstrated injury of the paraventricular nucleus in all. In most instances the nucleus of the tuber had also been damaged. Both nuclei proved to be intact in all the negative cases. In one case the pituitary had been completely destroyed by the capillary tube, but diabetes did not appear. Meningitis, compression, or some lesion at the base of the brain may affect the nucleus of the tuber, causing polyuria. A lesion in the walls of the third ventricle, or ependymitis, hemorrhage, or a tumor in the third ventricle may affect the paraventricular nucleus, producing glycosuria.—J. Am. M. Ass., **84,** 1157.

Dystrophia adiposogenitalis, with atypical retinitis pigmentosa and mental deficiency, possibly of cerebral origin. Cohen (S. S.) & Weiss (E.), Tr. Ass. Am. Physicians (Phila.), 1924, **39,** 356-358.

This is a report of an apparent familial predisposition to dystrophia adiposogenitalis. Four of 8 brothers and sisters were affected, presenting marked adiposity with mental deficiency, genital dystrophy, and atypical retinitis pigmentosa. The fat distribution was of the mammary and girdle type not corresponding exactly to hypophyseal obesity. The sella turcica was slightly smaller than normal in 2 of the children and within normal limits in the other 2. Two of the patients had 6 toes on the right foot.—I. B.

Pituitary syndromes (Contributo allo studio delle sindromi ipofisaire. Infantilismo ipofisario e diabete insipido). Ferrannini (L.), Arch. di patol. e clin. med. (Bologna), 1924, **3,** 113-153.

The author describes a syndrome of infantilism and diabetes insipidus in a boy 14 years old who had signs of involvement of both the anterior and posterior lobes of the pituitary gland, which, however, as indicated by roentgen examination of the sella turcica was not definitely increased in size. A thorough presentation of the case is given from the morphologic standpoint (Viola's anthropometric method) and from the biochemical standpoint, with particular consideration of the hydric exchange. In relation to the anterior lobe the patient showed: deficient stature, short and thin bones, lower extremities relatively long, arrest of development of the genital organs and absence of the secondary sexual characteristics, rough skin, and well developed intelligence. In relation to the postpituitary, the most essential sign was hydruria (from 14 to 19 liters of urine in 24 hours), in which the hydric excretion through the urine and the feces was superior to the amount of water introduced through the aliments. This was accompanied by polydipsia, which, if not satisfied, gave rise to serious phenomena of abstinence, intense intestinal stasis, marked increase in the elimination of chlorids, with alteration of carbohydrate metabolism. The polyuria was only temporarily reduced by the administration of pituitary extracts, especially by hypodermic injections of postpituitary preparations. After an elaborate critical review of the pathogenic theories of diabetes insipidus the author concludes that while in his case there was evidence of a lesion of the neurohypophysis, in many other cases diabetes insipidus depends on a lesion of the centers for diuresis located in the optopeduncular region and in the floor of the third ventricle. These centers function under the stimulus of the hypophyseal secretion which reaches the same by way of the infundibulum and the tuber cinereum. The diagnosis of the seat of the lesion in diabetes insipidus must be made in each clinical case from the consideration of the particular individual symptoms and of the concomitant syndromes, because polyuria may occur if the hormonic stimulus is lacking, if it cannot reach the centers of the diuresis because of defective canalization, or if the centers do not react to stimulation because of lesions within them.—Arch. Neurol. & Psychiat., **13**, 516.

Antagonistic action of posterior pituitary extract and insulin. Moehlig (R. C.) & Ainslee (Harriet B.), J. Am. M. Ass. (Chicago), 1925, **84**, 1398-1400.

From work performed on diabetic patients, Moehlig and Ainslee believe that pituitary extract injections improve the muscular asthenia to a great extent. This is true despite the fact that the patients, for the purpose of the work, are not placed on a diet. Patients with hypopituitarism suffer from asthenia, and fatigue is easily induced. The opposite is true in cases of hyperpituitarism. Posterior pituitary extract injected into normal rabbits produces, as

a rule, a slight rise in blood sugar. Posterior pituitary extract, when injected simultaneously with insulin, prevents the fall produced by the latter. Posterior pituitary extract, injected during insulin hypoglycemic convulsions, produces a rapid rise in blood sugar, with subsequent recovery of the rabbits. The point of attack of the pituitary extract seems to be in the periphery; viz., the skeletal muscle metabolism.—A. M. A.

Juvenile diabetes insipidus (Note cliniche, anatomiche e di patogenesi sul diabete insipido giovanile). Pincherle (M.) & Magni (L.), Arch. di patol. e clin. med. (Bologna), 1924, **3**, 261-289.

This is a study of 5 cases of diabetes insipidus in young persons. Two of the patients died from acute intercurrent disease, and came to necropsy. The authors, after a short but complete exposition of the different theories (endocrine, nervous, mixed) of diabetes insipidus and of the 5 clinical histories, give the anatomopathologic findings in the 2 cases, which seem to confirm the duality of the causes of the disease advanced in some of the pathogenic theories. In one case they found serious and extensive lesions of the hypophysis, with signs of active inflammatory reactions and advanced sclerosis, together with moderate neuroglial proliferation and slight degenerative lesions of the tuber cinereum. In the other case in which diabetes insipidus had been caused by what turned out to be a mild form of epidemic encephalitis, extensive and very severe degenerative lesions of the ganglionic cells of the tuber cinereum were found accompanied by intense phenomena of neuronophagia and perivascular infiltration, while the pituitary gland did not show any histologic alteration. These two diverse findings have led the authors to conclude in favor the dual neurohypophyseal conception in the pathogenic interpretation of the disturbed hydric exchange which is the basis of diabetes insipidus. In the majority of such cases the hypophysis or the tuberal centers or the important connections existing between the gland and the latter are altered, either separately or at the same time.—Arch. Neurol. & Psychiat., **13**, 520.

Pathology of the hypophysis. III. Chronic hypophysitis; fibrosis. Simonds (J. P.) & Brandes (B. S.), J. Am. M. Ass. (Chicago), 1925, **84**, 1408-1410.

It is evident from the 7 cases reported by Simonds and Brandes that, with advancing age, in many persons the hypophysis undergoes fibrosis, and the body does not receive the normal amount of the secretion of this gland. Fibrosis of the anterior lobe of the hypophysis occurs with moderate frequency in persons past 50. This condition is apparently due to arteriosclerosis of the vessels of the hypophysis. The character of the lesion is such that it must interfere with the function of the glandular portion of this organ. This

suggests one of the reasons for the failure of efforts at rejuvenation that are directed to the restoration of only one gland of internal secretion. One case of the series here reported appears to be true chronic hypophysitis. In spite of the negative Wassermann test, other findings in the body suggest the possibility of syphilis as its cause.—A. M. A.

Dystrophia adiposogenitalis, with atypical retinitis pigmentosa and mental deficiency. The Laurence-Biedl syndrome. Solis-Cohen (S.) & Weiss (E.), Am. J. M. Sc. (Phila.), 1925, **169**, 489-505.

Four of 8 brothers and sisters of Italian parentage exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the abnormal children showed polydactylism. The eye-grounds showed atypical retinitis pigmentosa. The fat distribution was largely of the girdle, mons and mammary type. A hypophyseal lesion could not be proved. Roentgen ray examinations of the sella region did not show conclusive changes. No anomaly of osseous development was found. Sugar tolerance tests did not indicate pituitary disease. Basal metabolism was below normal in 3 of the children. Both parents and children gave negative Wassermann reactions. The **thyroid** glands were palpable and within ordinary limits of size and consistency. There was no lymphadenopathy, and no history of rickets. The family history disclosed no marked adiposity, visual defect, polydactylism, deafness or idiocy. The 4 unaffected children seemed entirely normal; one, indeed, was uncommonly bright and active. Hormone therapy (pituitary-thyroid) seemed to correct amenorrhea in the older girl, but otherwise was without effect on any of the children. Subjective improvement in the sight of the elder girl may have been the result of hormone therapy, but may with equal probability be referred to suggestion, or to the general improvement of nutrition attending hospital care.—R. G. H.

Three cases of pernicious anemia and diabetes mellitus with a note on the apparent ineffectiveness of insulin in the presence of a profound anemia. Adams (S. F.), Med. Clin. N. Am. (Phila.), 1925, **8**, 1163-1170.

During the past 5 years there have been approximately 1000 patients with pernicious anemia at the Mayo Clinic, and approximately 2000 with diabetes mellitus; in only the 3 cases here reported were the two diseases combined. The author was able to find but one other instance of this combination in the literature, that of Parkinson, who, in 1910, observed a case of pernicious anemia terminating in acute diabetes. Insulin was apparently unable to reduce the blood sugar in 2 of the patients reported.—I. B.

Insulin. Banting (F. G.), Internat. Clin. (Phila.), 1924, **4**, S. 34, 109-116.

A brief outline of the principles underlying the action and use of insulin. The pathologic physiology occurring in diabetes mellitus is discussed. The necessity for co-operation between physician and patient is particularly stressed, including the need for a knowledge by the patient of the methods of urinalysis, preparation of a diabetic diet, and the knowledge as it pertains to symptoms and treatment of overdosage of insulin. In instances of diabetes with tuberculosis, insulin enables the use of proper nourishment with which to combat the tubercular infection. Patients generally regarded as bad surgical risks may be properly protected from the accidents of anesthesia by the use of insulin. Regardless of the severity of the disease it has been found that by carefully adjusted diet and dosage of insulin, all patients may be maintained sugar-free. This is a very fortunate circumstance, as there is ground for the belief that when the strain upon the pancreas is relieved there is regeneration of the islet cells of the organ. In some instances the sugar tolerance is increased to such a point that insulin is no longer required. Diabetes mellitus is fundamentally a disordered metabolism, primarily of carbohydrates, and secondarily of protein and fat. Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.—I. B.

Anhydremia with insulin and water intake. Drabkin (D. L.) & Shilkret (H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 369-371.

Doses of insulin were given to dogs, some of which had been water starved for several days and others of which had received 800 cc. of water per day. The authors note that dogs, desiccated through water-starvation, when given large doses of insulin developed a more severe anhydremia than the dogs which had water. Convulsions were not observed in the desiccated animals, although they invariably appeared in the others. Glucose did not prevent the death of the water-starved dogs. The non-desiccated animals immediately recovered after glucose administration.—J. C. D.

Diabetes mellitus, a contribution to its epidemiology based chiefly upon mortality statistics. Emerson (H.) & Larimore (L. D.), Trans. Ass. Am. Physicians (Phila.), 1924, **39**, 290-303.

The prevalence of diabetes mellitus in New York City is discussed. In 1866 there was recorded one death from diabetes for each 2437 deaths from other causes, but in 1923 there was one death from diabetes for each 51 deaths from other causes. The

increase in incidence and death rate from diabetes in this country, and in New York in particular, has been more rapid than that of any other disease for which we have records in the past 50 years. This increase is most marked among women of all ages, and among men and women over 35 years of age in particular. Persons of Semitic stock show the highest death rates, while the negroes show the lowest. It is not thought that the racial element is of fundamental importance since many elements of occupation, economic status, dietetic habits, etc., may be sufficient to explain the statistics in what may be fairly considered a disease of fatigued function in the great majority of cases. Seasonal variations in death rates, calculated upon a monthly basis, are apparently significant. This may or may not be due to seasonal incidence of intercurrent infections. Geographical distribution of the disease as measured by death rates in the United States appears to be explicable on the basis of differences in the age-grouping, race, economic status and occupation of the people, high rates being found where there is a high proportion of the population in the later decades of life, after 45 years, where there are many Jews, and where per capita wealth is high. Where life expectancy is high there is often a lower diabetic death rate than in states where life expectancy is low. It is believed that changes in food habits in the United States have contributed to the increase of diabetes, and that the higher carbohydrate element and greater food intake are the cause of overfatigue of the function of sugar tolerance.—I. B.

Observations on severe juvenile diabetes. Geyelin (H. R.) & Ladd (W. S.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 308-316.

This is a report of the progress of 9 instances of juvenile diabetic patients who have been under continuous treatment with insulin for 18 months or longer. No definite conclusions are drawn concerning the question of sugar tolerance under prolonged and continuous insulin treatment, though physical and mental well-being, once established, continues to exist, and the children are developing at approximately the same rate as the average normal child. The authors believe that every effort should be made to keep the patients as nearly sugar free as possible, and that continuous sugar freedom is the goal to be aimed at in the treatment of every case of diabetes.—I. B.

Heredity of diabetes. Hansen (S.), Ugesk. f. Læger (Copenhagen), 1924, **86**, 341-344.

The author considers diabetes as a hereditary disease. He believes that most cases are isolated because its origin depends upon a coincidence of disturbances rather than upon a single factor. This is illustrated by a series of genealogical tables.—K H. K.

Treatment of diabetes by raw fresh gland (pancreas). Hollins (T. J.), Brit. M. J. (Lond.), 1925, **i**, 503-504.

Hollins reports the successful use of fresh raw pancreas by mouth in the treatment of "about six" diabetics. A striking case is cited of an engineer with a severe attack, with ketonuria, who failed to improve under Allen treatment, who became sugar free and gained weight under raw gland treatment. His blood sugar fell to 0.13%. Marked glycosuria immediately recurred upon intermission of the treatment. The author insists that absolute freshness of the gland is essential to its efficacy. He believes that a tablespoon full (which is adequate dosage) every day or two is less distasteful to the patients than are frequent insulin injections.
—R. G. H.

Hypoglycemia. Jonas (L.), Med. Clin. N. Am. (Phila.), 1925, **8**, 949-956.

Hypoglycemia has become an important clinical entity since the discovery of **insulin.** Mild hypoglycemia may also be observed in **myxedema, cretinism, hypopituitarism, Addison's disease,** progressive muscular dystrophy, and following subtotal **thyroidectomy** for exophthalmic goiter. Weakness, sweating, rapid pulse, and nervous phenomena are the most outstanding clinical features of hypoglycemia. Treatment consists in the administration of carbohydrates.—I. B.

Pancreatic and hepatic activity in diabetes mellitus. Jones (C. M.), Castle (W. B.), Mulholland (H. B.) & Bailey (F.), Arch. Int. Med. (Chicago), 1925, **35**, 315-336.

An unselected group of 68 diabetic patients has been examined for evidence of alteration in pancreatic or hepatic activity. Pancreatic enzyme activity was diminished in nearly one-half of the cases. Bile pigment elimination in the duodenal contents was abnormally high in about three-fourths of the cases. In nearly one-third of the cases there were associated enzyme and pigment abnormalties. The greatest alterations in enzyme activity were noted in the lipolytic and proteolytic ferments. These findings are taken to indicate that in diabetes mellitus there is a marked alteration in the external secretory activity of the pancreas and in the hepatic function. The enzyme abnormalities are probably due to associated anatomic and functional changes in the acinar tissue of the pancreas. Undernutrition may play a part in the production of such changes, but it is not the sole cause. Such alterations in pancreatic or liver function may well contribute to the symptomatology of diabetes. It is suggested that the diminution of enzyme activity may result in disturbances due to improper digestion of fat and protein. Undernutrition, of the several variable factors entering

into an uncomplicated case of diabetes, evidently places the greatest strain on the liver, and results in striking bile pigment abnormalities. Undernutrition should therefore be avoided, on account of its undesirable effects on liver and pancreatic function. Efficient insulin therapy, with its associated increase in food intake and improvement of tissue function, seems to be associated with a reduction in pancreatic and hepatic abnormalities. Cases of diabetes complicated by pancreatic disease were found to be associated with an increased frequency of pancreatic enzyme disturbance. Sepsis, gangrene, and pancreatitis seemed to be predominating factors in producing an alteration in bile pigment metabolism. All three patients with hemochromatosis showed a reduction in enzyme activity, but no abnormality in pigment elimination. Acidosis produces a marked disturbance of pancreatic enzyme activity and liver function. The improvement in pancreatic and hepatic function, as measured by changes in the enzyme activity and bile pigment elimination, following recovery from acidosis, is very striking, and illustrates the degree to which acidosis affects all bodily functions. Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19% of the cases in this series. The sediment findings by which such a diagnosis can be made are characteristic, and have been previously described. In addition, several other patients had histories or operative findings consistent with the diagnosis of gallstones. The average age of this group of cases, constituting 22% of the entire series, was about 51. The authors believe that the existing figures for the incidence of gallstones in diabetes is far too low. It would not be surprising to find that at least one-fifth of all diabetic patients over 40 have an associated cholelithiasis. In adults, cholelithiasis is probably one of the most important etiologic factors in diabetes mellitus. For this reason, it would seem that surgical intervention in all cases of gall-bladder disease, in the absence of other complication, is indicated as a means of preventing the occurrence of diabetes, or of relieving an existing diabetes.—Authors' summary.

The changing diabetic clientele. Joslin (E. P.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 304-307.

Joslin states that a new race of diabetics has come upon the scene, in that the duration of the diabetes among patients entering the hospital for treatment during 1923 was 5.6 years, 2 years greater than in 1921 and 1922. The duration of the disease among these living diabetics exceeded by a year the entire duration of diabetes among all Joslin's fatal cases up to the year 1914. The diabetics of today are 11 years older than those of a decade ago, and since they represent to an extent a milder type of the disease, this would indicate an increased zeal on the part of the medical profession in the diagnosis of early cases. The prevention of diabetes is as im-

portant as the prevention of an infectious disease. Prophylaxis is possible because it is known to be 15 times as frequent among adults, it is 10 to 20 times as common among the fat, it is 2½ times as common among Jews, and slightly more so among Jewish females. A campaign to eradicate diabetes should therefore yield maximum returns if directed toward its prevention and discovery in adult, fat females, and particularly in Jews. However, a Jewish child is no more prone to diabetes than the child of a Gentile. Insulin has exceeded expectations and coma is relieved far more surely than was the case heretofore. Moreover, the educational value of insulin is of vital importance, there having been promoted among physicians and patients a profound consideration of details in diet and a respect for scientific medicine.—I. B.

Action of insulin on the central nervous system (Zur Wirkung des Insulins auf das Zentralnervensystem). Kleitman (N.) & Magnus (R), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 148-154.

For occurrence of convulsions after insulin injections into rabbits (and cats) presence of the medulla oblongata is necessary. Cerebrum, thalami, forepart of middle-brain and labyrinth are unnecessary. The hypoglycemia produces independently (a) stimulation of motor centres in the medulla, followed by convulsions, (b) stepwise paralysis of the position reflexes and certain labyrinth reflexes, though the majority of these remain unaffected, and (c) cessation of breathing.—A. T. C.

Examinations on the manner of effect of insulin. Lundsgaard (C) & Hollböll (S. A.), Ugesk. f. Læger (Copenhagen), 1924, **86**, 591-597; 693.

The authors describe a method (dialysis through certain collodion membranes) of producing clear solutions of glucose to which there can be added non-transparent materials, for instance, blood. They have shown that by adding pure insulin or insulin and fresh blood to solutions of glucose there can be produced a change in polarization of the solution. If blood sugar in normal persons is found in the Gamma form the Beta glucose absorbed through the intestinal tract cannot be changed to Beta in the blood; the conversion is brought about by some extravascular process. It is shown that ordinary Beta glucose is changed into the Gamma form by addition of insulin together with muscular tissue in vitro. The effect of different factors (glucose concentration, amount of insulin, amount of muscular tissue, temperature) in the process is studied quantitatively. The muscular tissue must be fresh; its efficacy disappears in 2 hours. Its activity must therefore be conditioned by vital processes of the cells. By repeated fractional addition of insulin and muscular tissue to the same solution of glucose the concentra-

tion of the Gamma form can be raised to 76% of the total amount of glucose. The conversion process is reversible, but only very slowly. Addition of normal gastric juice to a solution containing Gamma glucose does not accelerate the reverse conversion.

—K. H. K.

On the mechanism of insulin action. Mueller (E. F.), Wiener (H. J.) & Wiener (Renee von E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 375-382.

Insulin was injected subcutaneously and intracutaneously in normal human subjects and the fall in blood sugar was studied. It was more rapid following the intracutaneous injection. In rabbits blocking the nerves to the skin area injected abolishes the difference between the results from the two methods. Absorption is slower in the case of the intracutaneous injections, but the fall in blood sugar in these cases begins before the hormone can be effective through the blood, i. e., 20 minutes after injection. The authors believe, therefore, that there is a nervous stimulation from the injected area, probably through the parasympathetic system, which inhibits glycogen formation, thus bringing about an initial fall in blood sugar. Later the direct hormonal effect appears and overshadows this first reduction.—J. C. D.

Five cases of diabetes and coma. I. The effect of three attacks of coma upon tolerance. II. Infection and coma. III. An obscure case of coma. IV. Coma due to cerebral hemorrhage simulating diabetic coma. V. Renal insufficiency simulating diabetic coma. Murphy (W. P.), Med. Clin. N. Am. (Phila.), 1925, **8**, 1517-1528.

Acidosis with coma may have a very acute onset and be precipitated by infections, dietary indiscretions, or lack of proper cooperation in diabetic treatment. The CO_2 combining power of the blood is a more reliable index of the degree of acidosis than the urinary diacetic reaction. It is dangerous to make the diagnosis of diabetic coma in cases without a lowered alkali reserve. There is usually a relatively high red and white blood count in coma cases. The blood changes are probably due to the dehydration, which may be marked in acidosis. The author emphasizes the practical details in the management of cases of diabetes with severe acidosis or in coma.—I. B.

Severe acidosis of diabetes. Musser (J. H., Jr.), Med. Clin. N. Am. (Phila.), 1925, **8**, 775-779.

Tuberculosis does not occur in diabetics more often than in non-diabetics. When the two diseases are associated the problem is serious, and it is more important to treat the diabetes than the tuberculosis. It is especially with the aid of insulin that the patient

may be sufficiently nourished and made sugar free. Intelligent co-operation is a valuable asset.—I. B.

Experimental researches on the pathogenesis of ketosis. Petren (K.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 317-319.

Basing his opinion upon studies carried on during a period of 13 years, the author concludes that it is best to give only a small amount of protein in grave diabetes (1-3 to 1-4 gram per kilo of body weight, or even smaller amounts). On the other hand, there is no danger in giving the amount of fat that corresponds to the requirement of the nutrition. He found such lowering of the protein of the food to be the best way of reducing hyperglycemia and ketosis.—I. B.

Insulin in diabetes requiring surgery. Petty (O. H.) & LeFevre (W. M.), Med. Clin. N. Am. (Phila.), 1925, **8**, 919-930.

A valuable contribution on the subject, with several case histories. Of the 31 diabetes patients operated upon, 7 required foot and leg amputations, and of these there were 3 fatalities. Patients requiring over 70 units of insulin daily possess some complication, probably a focus of infection inhibiting the action of insulin. Removal of the infection enhances the effect of insulin. Surgical technic does not differ from that used in non-diabetic patients. Close co-operation between internist and surgeon is essential in these cases. Preoperative diabetic treatment is either an emergency or a routine procedure, depending upon existing indications. Postoperative diabetic management is likewise of utmost importance. Postoperative acidosis is prevented by the use of carbohydrates, liquids and insulin.—I. B.

Age as a factor in diabetic mortality. Thomason (J. W.), Boston M. & S. J., 1925, **192**, 532-536.

Careful study of statistics leads the author to conclude that in comparing diabetic with general mortality it is manifest that the diabetic mortality reaches two distinct elevations, a peak and a plateau. The peak occurs at the age of fifteen years and is a relative increase, while the second, the plateau, develops between sixty and seventy years of age and is an actual increase. The diabetic mortality curve begins to rise rapidly at from forty-five to fifty years of age, reaching its maximum at eighty years for all four decades and then rapidly falls.—J. C. D.

Results following the extirpation of the pineal gland in newly hatched chicks. Badertscher (J. A.), Anat. Record (Phila.), 1924, **28**, 177-197.

The operation was performed on White Leghorn chicks 4-5

days after hatching. The gland was removed completely from 5 cockerels and 6 hens and only partially removed from 5 cockerels and 9 hens. The latter served as traumatized controls; 9 cockerels and 16 hens served as normal controls. The chickens were weighed at regular intervals and observations made on the development of the primary and secondary sex characters (crowing, comb, sexual instinct). Growth curves were constructed from the average rate of growth for each group. At the termination of the experiments the testicles and combs of the males of all groups were weighed for comparison. Badertscher believes that his results can all be interpreted as negative. His results are contradictory to the prevailing notion that pineal gland deficiency results in a precocious somatic and sexual maturity.—W. J. A.

Exophthalmic goiter in children. Burnet (J.), Internat. Clin. (Phila.), 1925, **1**, S. 35, 94-96.

A brief discussion of the etiology of exophthalmic goiter in children, and the report of a case in a female child of 9 who apparently recovered under treatment consisting essentially of the administration of tincture of iodine.—I. B.

Lymphoid hyperplasia in the thyroid gland. Caldwell (G. T.), South. M. J. (Birmingham), 1925, **18**, 177-180.

This is a condition which has been previously described. It is known in its extreme form as Riedel's struma, which is characterized by a markedly increased density of the gland. Twenty-nine cases have been seen in 5 years in general hospital practice, so it is more frequent than is usually stated. All were in women. Three only were of the extreme type. The condition was not regularly associated with infections in other parts of the body.—J. C. D.

Surgical aspects of goiter. Frazier (C. H.), Atlantic M. J. (Harrisburg), 1925, **28**, 376-385.

Except from the standpoint of preoperative preparation, the differentiation between toxic adenoma and exophthalmic goiter is, insofar as the successful management is concerned, a matter of little moment. Basal metabolism determinations are important. Frazier does not agree with Crile that the metabolic rate is not a guide to operability. He is thoroughly convinced that surgical therapy is the most effective means of arresting the symptoms of toxic goiter. He quotes from his own records, deduced from reports on questionnaires sent out to patients, in which 27% of his patients are reported as being "entirely well" and 73% as "improved." The correction of serious cardiac disturbances is an important preoperative procedure. Digitalization may be resorted to and may be continued during the first few postoperative days. The fractional

method of operating in bad risk cases is essential. The psychological factor in the preparation of the patient is a vital therapeutic procedure. A persistent thymus should receive x-ray treatment for 2 weeks before operation. There is always danger of damage to the recurrent laryngeal nerves. This can be overcome by grasping the vessels at the inferior pole close to the capsule, and by the avoidance of resection of the lobe on its mesial aspect below the level of the trachea. Paralysis of the recurrent laryngeal nerve not only results in dyspnea, aphonia, and in the pulmonary complication of the operation, but occasionally in death on the operating table. Transfusion by the citrate method following operation adds to the safety of the patient. If there is perfect teamwork on the part of the operating surgeon and his assistants the death rate appears negligible. There was no mortality associated with the series of 185 operations reported by Frazier.—I. B.

Influence of the thyroid gland on the increased heat production occurring during pergnancy and lactation. Marine (D.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 180-190.

As a result of observations on rabbits, the author concludes that there is probably an increase in the metabolism of the pregnant woman that cannot be accounted for entirely on the basis of the active protoplasmic mass of the fetus; that the heat production during lactation remains elevated, though this increase is less than half of that present before parturition, and that the maternal thyroid, through its increased functional activity, increases heat production during pregnancy and lactation. Marine believes that these findings partly explain why pregnancy and lactation constitute one of the three important periods in life when simple goiter develops.
—I. B.

Iodine therapy in toxic goiter. Mason (E. H.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 167-179.

Basing his remarks on data of 8 detailed case histories, the author believes that in exophthalmic goiter iodine administration is an important step in therapeusis, especially in preoperative management.—I. B.

Goiter in the intermountain region of Utah. Middleton (G. W.), J. Am. M. Ass. (Chicago), 1925, **84**, 1172-1173.

The larger phase of the goiter problem, and the one that may prove to be most significant in the future, Middleton says, is the relative iodin deficiency in the various geological strata that form the catchment basins and water sheds of the streams. If this were determined in any given section, one could at a glance estimate the probable goiter incidence and the extent of prophylactic measures

necessary to meet the situation. Theoretically, all volcanic or granitic sections of country should have a relatively large percentage of goiter incidence. Whether this is the case remains to be proved, but in the data available in the intermountain region of Utah there is at least a marked indication in that direction. Thus, in the town of St. George, in Southern Utah, with a population of more than 3,000, goiter was quite unusual for more than half a century, from the time of its founding until a water system was installed and the water from the Pine Valley Mountains brought in. Pine Valley Mountains are almost entirely igneous, and the volatile iodin no doubt escaped at the time of their extrusion. Since the advent of the new water supply, many people have developed goiter, and what was for a long time a comparatively immune district has now been added to the large endemic section of Southern Utah. In the Virgin Valley, which is a part of this section, fully 75% of the adult women have goiter. It is here, in these isolated mountain gorges, that one encounters enormous thyroid growths, which are allowed to progress unchallenged until they assume maximal dimensions. It seems to be well established by the statewide survey now in progress that towns which enjoyed considerable immunity from goiter while they used well water, and water from the surface springs are taking on a marked increase of goiter incidence since they installed water systems, and are getting their water supply from mountain springs up near the melting snows. During the past 3 years Middleton has treated 333 cases of the various forms of goiter, not including hypothyroidism or the inflammatory conditions. One hundred and fifty-six thyroidectomies were performed with 2 fatalities, a mortality of 1.3%. Seventy-three percent of these patients were toxic, and many of them extremely toxic. One of these fatalities was due to tracheal obstruction, and one patient was so toxic that she showed no improvement after months of rest and medical treatment, and thyroidectomy was undertaken as a last resort. Middleton believes that rest in bed with abundance of fluids, and the use of compound solution of iodin in the hyperplastic cases are the most important preparatory measures. Except in cases with broken compensation, preoperative digitalization has been of little value. Calcium carbonate is given to prevent tetany. The condition described as hypoglycemia has been encountered five or six times. Urinalysis showed much acetone and diacetic acid. The relief from intravenous glucose was striking.—A. M. A.

Iodine in the treatment of goiter. Plummer (W. A.), Med. Clin. N. Am. (Phila.), 1925, **8**, 1145-1151.

In goiters containing adenomatous tissue, iodine administration, especially after the adolescence, may engender hyperthyroidism. Even the minute quantities of iodine present in iodized salt or in the water supply may have the same effect. Thyroid

administration under similar conditions is not so likely to yield hyperthyroidism, although adenomatous tissue is seldom reduced by this substance. In the Mayo Clinic, 10 minims of Lugol's solution are administered 3 times a day for at least 7 days prior to thyroidectomy. In patients with crisis or near crisis, 50 minims are given during the first 2 or 3 hours by mouth or by rectum, depending upon conditions. If the patient is in crisis 50 minims are administered again during the following forenoon. Patients with postoperative recurrences are given 10 minims daily over an indefinite period with intervals of cessation of the drug and readministration if necessary. The operative mortality with the use of Lugol's solution has been reduced 2% or more.—I. B.

Syphilis of the thyroid gland, with special reference to exophthalmic goiter. Schulmann (E.), Internat. Clin. (Phila.), 1924, 4, S. 34, 126-136.

A useful survey of syphilis as an etiological factor in exophthalmic goiter. Ewald's theory that the thyroid enjoys a kind of immunity to syphilis on account of its iodine content can no longer be maintained. Following a brief discussion on syphilis as productive of myxedematous states, the author quotes Pierre Marie and others to substantiate his views that lues is not an unknown causal factor in exophthalmic goiter. Two types of the tertiary syphilis of the thyroid gland are recognized: (1) gummatous thyroiditis, which is the most common, and (2) interstitial or sclerogummatous thyroiditis. Schulmann presents 3 illustrative case histories. Syphilitic exophthalmic goiter usually develops without any special predisposition, and one does not ordinarily find those neuropathic taints upon which much stress is laid in the usual forms of the Basedowian syndrome. The time elapsing between the incidence of syphilis and the development of exophthalmic goiter varies greatly. Sometimes the symptoms may develop during the secondary phase of the syphilis, at other times during the tertiary phase. In one case of the author's, exophthalmic goiter developed 23 years after the onset of syphilis. Occasionally the Basedowian syndrome may appear during the evolution of tabes dorsalis, thus showing the simultaneous tardy influence of the spirachetae, both on the posterior columns of the spinal cord and the endocrine glands. The symptomatology of this type of exophthalmic goiter does not differ from the usual form. The syndrome usually develops progressively and in many instances is for a considerable period of time unnoticed by the patient. Specific treatment applied to the syndrome resulting from lues is frequently quite successful and is a criterion of the highest order in the discrimination between this and the ordinary types of exophthalmic goiter. —I. B.

Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency. Warfield (L. M.) & Youmans (J. B.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 130-135.

Injury to the liver may occur in extremely severe cases of thyrotoxicosis, and jaundice has been regarded as a grave prognostic sign. It has recently been suggested that diminished sugar tolerance occurring in thyrotoxicosis may be due to liver damage. As the result of a combined study of the functional efficiency of the liver and of the glucose tolerance in cases of thyrotoxicosis, the authors find that injury to the liver occurs in a surprisingly large number of instances. Of the 30 cases studied, 12 showed evidence of injury to the liver according to the phenoltetrachlorphthalein test of Rosenthal. Jaundice occurred in 3 instances, and was associated with the most marked evidence of liver damage observed. Hepatic damage bears no constant relationship to the sugar tolerance, basal metabolic rate, loss of body weight, or other known factors concerned in this disease.—I. B.